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United States Government Accountability Office

GAO

Report to the Ranking Member, Committee on Rules, House of Representatives

September 2011

ANTIBIOTIC RESISTANCE

Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals

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GAO-11-801

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GAO Accountability * Integrity * Reliability

Highlights

Highlights of GAO-11-801, a report to the Ranking Member, Committee on Rules, House of Representatives

Why GAO Did This Study

Antibiotics have saved millions of lives, but antibiotic use in food animals contributes to the emergence of resistant bacteria that may affect humans. The Departments of Health and Human Services (HHS) and Agriculture (USDA) are primarily responsible for ensuring food safety. GAO reviewed the issue in 2004 and recommended improved data collection and risk assessment. GAO was asked to examine the (1) extent to which agencies have collected data on antibiotic use and resistance in animals, (2) actions HHS's Food and Drug Administration (FDA) took to mitigate the risk of antibiotic resistance in humans as a result of use in animals, (3) extent to which agencies have researched alternatives to current use practices and educated producers and veterinarians about appropriate use, and (4) actions the European Union (EU) and an EU member country, Denmark, have taken to regulate use in animals and lessons that have been learned. GAO analyzed documents, interviewed officials from national organizations, and visited producers in five states and Denmark.

What GAO Recommends

GAO recommends that HHS and USDA (1) identify and evaluate approaches to collecting detailed data on antibiotic use in animals and use these data to evaluate FDA's voluntary strategy, (2) collect more representative data on resistance, and (3) assess previous efforts on alternatives to identify where more research is needed. HHS and USDA agreed with GAO's recommendations.

View GAO-11-801 or key components.
For more information, contact Lisa Shames at (202) 512-3841 or shamesl@gao.gov.

What GAO Found

HHS and USDA have collected some data on antibiotic use in food animals and on resistant bacteria in animals and retail meat. However, these data lack crucial details necessary to examine trends and understand the relationship between use and resistance. For example, since GAO's 2004 report, FDA began collecting data from drug companies on antibiotics sold for use in food animals, but the data do not show what species antibiotics are used in or the purpose of their use, such as for treating disease or improving animals' growth rates. Also, although USDA agencies continue to collect use data through existing surveys of producers, data from these surveys provide only a snapshot of antibiotic use practices. In addition, agencies' data on resistance are not representative of food animals and retail meat across the nation and, in some cases, because of a change in sampling method, have become less representative since GAO's 2004 report. Without detailed use data and representative resistance data, agencies cannot examine trends and understand the relationship between use and resistance.

FDA implemented a process to mitigate the risk of new animal antibiotics leading to resistance in humans, which involves the assessment of factors such as the probability that antibiotic use in food animals would give rise to resistant bacteria in the animals, but it faces challenges mitigating risk from antibiotics approved before FDA issued guidance in 2003. FDA officials told GAO that conducting postapproval risk assessments for each of the antibiotics approved prior to 2003 would be prohibitively resource intensive, and that pursuing this approach could further delay progress. Instead, FDA proposed a voluntary strategy in 2010 that involves FDA working with drug companies to limit approved uses of antibiotics and increasing veterinary supervision of use. However, FDA does not collect the antibiotic use data, including the purpose of use, needed to measure the strategy's effectiveness.

HHS and USDA have taken some steps to research alternatives to current antibiotic use practices and educate producers and veterinarians on appropriate use of antibiotics. However, the extent of these efforts is unclear because the agencies have not assessed their effectiveness. Without an assessment of past efforts, the agencies may be limited in their ability to identify gaps where additional research is needed. Except for one $70,400 USDA project, all other federal education programs have ended.

Since 1995, the EU, including Denmark, banned the use of antibiotics to promote growth in animals, among other actions. Some of their experiences may offer lessons for the United States. For example, in Denmark, antibiotic use in animals initially decreased following a series of policy changes. The prevalence of resistant bacteria declined in food animals and retail meat in many instances, but a decline in humans has only occasionally been documented. Denmark's data on use and resistance helped officials track the effects of its policies and take action to reverse unwanted trends. The EU faces difficulty collecting data that can be compared across countries, but officials there said such data are needed to fully understand how use in animals may lead to resistance in humans.

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Abbreviations

ADUFA	Animal Drug User Fee Amendments of 2008
APHIS	Animal and Plant Health Inspection Service
ARMS	Agricultural Resource Management Survey
ARS	Agricultural Research Service
CAHFSE	Collaboration in Animal Health and Food Safety Epidemiology
CDC	Centers for Disease Control and Prevention
CIPARS	Canadian Integrated Program on Antimicrobial Resistance Surveillance
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Program
ERS	Economic Research Service
EU	European Union
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
HACCP	Hazard Analysis and Critical Control Points
HHS	Department of Health and Human Services
MRSA	methicillin-resistant *Staphylococcus aureus*
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NIFA	National Institutes of Food and Agriculture
NIH	National Institutes of Health
NOP	National Organic Program
USDA	U.S. Department of Agriculture
VFD	veterinary feed directive
WHO	World Health Organization

GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

September 7, 2011

The Honorable Louise M. Slaughter
Ranking Member
Committee on Rules
House of Representatives

Dear Ms. Slaughter:

Antibiotics have saved millions of lives by controlling infectious diseases, but the continued effectiveness of these drugs is now jeopardized by the emergence of bacteria resistant to antibiotics, according to the World Health Organization (WHO). Antibiotic-resistant infections can result in the use of more expensive drugs for treatment, longer hospital stays, and even death. In addition, the speed at which antibiotic resistance is rendering these drugs ineffective far outpaces the development of new antibiotics, according to WHO. Potential contributors to antibiotic-resistant infections in humans include the widespread use of antibiotics in human medicine, the presence of antibiotics in the environment, and the use of antibiotics in animals raised for human consumption—often referred to as food animals—such as cattle, swine, and poultry.

Antibiotics are an integral part of animal production in the United States and many other countries. According to food animal producers, antibiotic use reduces the cost of producing animals and, therefore, the price consumers pay for food. Antibiotics are used to treat animal diseases; to prevent and control the spread of diseases during phases of production when animals are at an increased risk of illness, such as weaning; and to increase animals' growth rate. Public health officials are particularly concerned about the use of antibiotics to promote growth because such antibiotics are administered in low doses over long periods to large groups of healthy animals, which can cause animals to become reservoirs of antibiotic-resistant bacteria. Once the resistant bacteria develop in food animals, they may be passed to humans through the consumption or handling of meat or other animal-derived food products, contact with animals by farm workers or food processors, or runoff of animal waste into soil or water.

Two federal departments are primarily responsible for ensuring the safety of the food supply, including the safe use of antibiotics in food animals—the Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA). Within HHS, the Food and Drug

Administration (FDA) approves for sale, and regulates the manufacture and distribution of, antibiotics used in animals. USDA collects information about antibiotic use and resistance in food animals, funds research related to antibiotic resistance, and educates producers and other users about appropriate antibiotic use.

In April 1999, we reported on federal responsibilities related to tracking and overseeing antibiotic use in food animals and noted that, despite more than two decades of discussion, federal agencies had not reached agreement on the safe use of antibiotics in food animals.[1] We recommended that agencies develop and implement a plan to evaluate the risks and benefits of the existing and future use of antibiotics in agriculture. Subsequently, in 1999, HHS created the Interagency Task Force on Antimicrobial Resistance to coordinate federal efforts to address antibiotic resistance in humans and animals. This task force developed *A Public Health Action Plan to Combat Antimicrobial Resistance* in January 2001 to serve as a blueprint for federal coordination to address antibiotic resistance.

In April 2004, we again reviewed the issue of antibiotic use in food animals and made two recommendations: that FDA expedite its risk assessments of the extent to which antibiotic use in food animals poses a risk to human health, and take mitigating action, if necessary; and that HHS and USDA jointly develop and implement a plan for collecting data on antibiotic use in animals.[2] HHS and USDA generally agreed with our findings, but neither has implemented the recommendations, though both departments continued independent data collection efforts rather than working jointly to develop and implement a plan. Furthermore, we reported that countries in the European Union (EU), in particular Denmark, were taking significant steps to restrict the use of antibiotics in animals and that many countries, including Denmark and Canada, collect detailed data on antibiotic use in animals.

[1]GAO, *Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health*, GAO/RCED-99-74 (Washington, D.C.: Apr. 28, 1999).

[2]GAO, *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals*, GAO-04-490 (Washington, D.C.: Apr. 22, 2004).

In 2007, we added food safety to our list of high-risk areas that warrant attention by Congress and the executive branch. Our biennial reviews of high-risk issues in 2009 and 2011 concluded that fragmentation of federal food safety oversight continues to be a problem.[3] We have made several recommendations on this issue, including recommending that agencies develop a government-wide performance plan for food safety that includes results-oriented goals and performance measures, as well as information about strategies and resources.[4]

In this context, you asked us to evaluate federal efforts to address risks from antibiotic use in food animals. Our objectives were to determine (1) the extent to which federal agencies have collected data on antibiotic use and resistance in food animals, (2) the actions FDA has taken to mitigate the risk of antibiotic resistance in humans as a result of antibiotic use in food animals, (3) the extent to which federal agencies have conducted research on alternatives to current antibiotic use practices and educated producers and veterinarians about appropriate antibiotic use, and (4) what actions the EU and an EU member country, Denmark, have taken to regulate antibiotic use in food animals and what lessons, if any, have been learned.

In conducting our work, we reviewed documents related to antibiotic use in food animals, including applicable laws; federal plans, regulations, and guidance; and federal reports on antibiotic use, resistance, research, and education. We also interviewed and collected documentation from officials at HHS and USDA. In addition, we conducted structured interviews with representatives of a nonprobability sample of 11 national organizations representing producers of food animals, pharmaceutical companies, and public health organizations. Representatives of these organizations, who spoke on behalf of their members, answered questions about federal efforts to collect data on antibiotic use and resistance, conduct research on alternatives to antibiotics, and educate producers and veterinarians. We selected these organizations because of their expertise in topics surrounding antibiotic use in animals and

[3]See, most recently, GAO, *High-Risk Series: An Update*, GAO-11-278 (Washington, D.C.: February 2011).

[4]See: GAO, *Federal Food Safety Oversight: Food Safety Working Group Is a Positive First Step but Governmentwide Planning Is Needed to Address Fragmentation*, GAO-11-289 (Washington, D.C.: Mar. 18, 2011).

resistance. Furthermore, we conducted a structured interview of a nonprobability sample of five representatives of national veterinary organizations about federal efforts to conduct research on alternatives to antibiotics and educate producers and veterinarians, as well as any efforts they may have undertaken to address these issues. We sought to include a variety of organizations with perspectives about antibiotic use and resistance; however, the views of organizations consulted should not be considered to represent all perspectives about these issues and are not generalizable. In addition, we conducted site visits with conventional and alternative (either organic or antibiotic-free) producers of poultry, cattle, swine, and dairy products to obtain a better understanding of production practices; the types of antibiotic use data available at the farm level; and perspectives on federal efforts to educate producers about antibiotics. During these site visits, we also spoke with veterinarians involved with food animal production.

To identify actions the EU and Denmark have taken regarding antibiotic use in food animals, we met with EU and Danish government officials, veterinarians, and producer organizations. We selected the EU and Denmark because they implemented bans on growth promotion uses of antibiotics in 2006 and 2000, respectively, which allows for a review of the effects of these policies in the years since. In addition, we reviewed documents detailing the results of EU and Danish policy actions and interviewed Danish producers and veterinarians at conventional poultry and swine farms to learn about their experiences implementing government regulations on antibiotic use. A more detailed description of our objectives, scope, and methodology is presented in appendix I.

We conducted this performance audit from August 2010 to September 2011, in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Antibiotics are substances that destroy microorganisms or inhibit their growth; they have been used for 70 years to treat people who have bacterial infections. In this report, the term antibiotic is used to refer to any substance used to kill or inhibit microorganisms, also sometimes referred to as an antimicrobial. Resistance to penicillin, the first broadly used antibiotic, started to emerge soon after its widespread introduction.

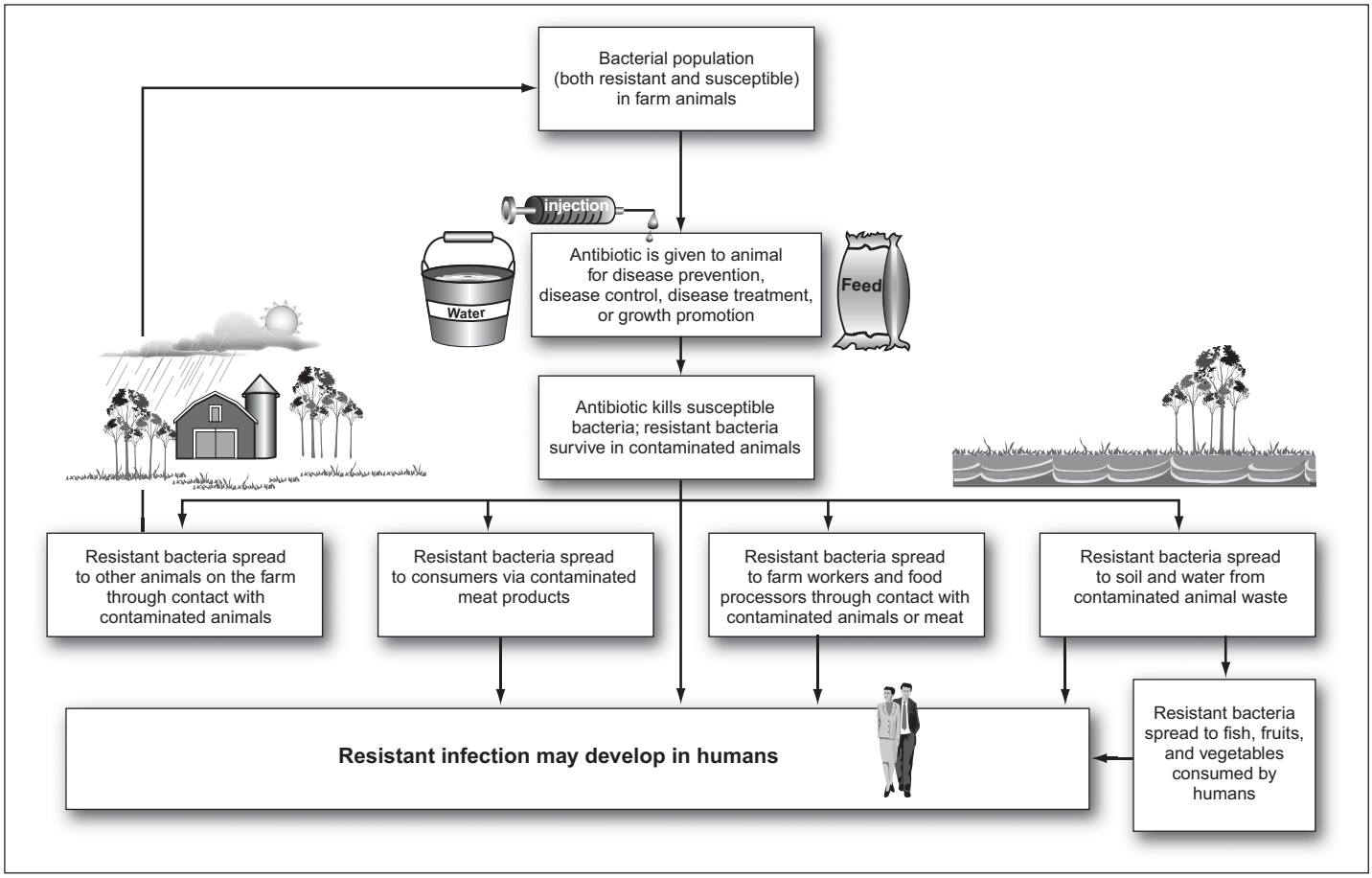
Since that time, resistance to other antibiotics has emerged, and antibiotic resistance is becoming an increasingly serious public health problem worldwide.

Antibiotic-Resistant Bacteria Can Spread through a Number of Pathways

Bacteria acquire antibiotic resistance through mutation of their genetic material or by acquiring genetic material that confers antibiotic resistance from other bacteria. In addition, some bacteria developed resistance to antibiotics naturally, long before the development of commercial antibiotics. Once bacteria in an animal or human host develop resistance, the resistant strain can spread from person to person, animal to animal, or from animals to humans.

Antibiotic-resistant bacteria can spread from animals and cause disease in humans through a number of pathways (see fig. 1). For example, unsanitary conditions at slaughter plants and unsafe food handling practices could allow these bacteria to survive on meat products and reach a consumer. Resistant bacteria may also spread to fruits, vegetables, and fish products through soil, well water, and water runoff contaminated by fecal matter from animals harboring these bacteria. If the bacteria are disease-causing, the consumer may develop an infection that is resistant to antibiotics. However, not all bacteria cause illness in humans. For example, there are hundreds of unique strains of *Escherichia coli* (*E. coli*), the majority of which are not dangerous. Indeed, while some strains of *E. coli* are dangerous to humans, many *E. coli* bacteria strains are a normal component of human and animal digestive systems.

Figure 1: Potential Pathways for Spread of Antibiotic-Resistant Bacteria from Animals to Humans



Sources: GAO; Art Explosion (human figures).

Note: This figure is not intended to represent the full complexity of resistance transmission. For example, antibiotic-resistant bacteria can also be transferred from humans to animals.

Antibiotics Are Currently Used in Food Animal Agriculture

The use of antibiotics in animals poses a potential human health risk, but it is also an integral part of intensive animal production in which large numbers of poultry, swine, and cattle are raised in confinement facilities. Over time, food animal production has become more specialized and shifted to larger, denser operations, known as concentrated animal feeding operations. According to a 2009 USDA study, *The Transformation of U.S. Livestock Agriculture: Scale, Efficiency, and Risks*, this shift has led to greater efficiencies in agricultural productivity—meaning more meat and dairy production for a given commitment of land, labor, and capital

Dairy Production

Source: GAO.

Modern dairy production is diverse, ranging from cows housed indoors year-round to cows maintained on pasture nearly year-round. In the United States, milk comes primarily from black and white Holstein cows genetically selected for milk production. Over the years, the concentration of more cows on fewer farms has been accompanied by dramatic increases in production per cow, arising from improved genetic selection, feeds, health care, and management techniques. Expansion to larger herd sizes has also allowed producers to increase the efficiency of production and capitalize on economies of scale. When a cow is no longer able to breed and produce milk, it is usually sold to the market as beef. According to the National Milk Producers' Federation, dairy producers use antibiotics to treat mastitis, an inflammation of the udder, and other diseases. Any milk produced during antibiotic treatment, and for a specific withdrawal period after treatment has ceased, must be discarded in order to prevent antibiotic residues in milk. This discarded milk imposes an economic cost to dairy producers, so producers generally avoid treating dairy cows with antibiotics when possible. According to the National Milk Producers' Federation, dairy producers do not use antibiotics for growth promotion that are medically important in human medicine.

resources—and lower wholesale and retail prices for meat and dairy products. However, the study notes larger farms with higher concentrations of animals may be more vulnerable to the rapid spread of animal diseases, which producers may combat by using antibiotics. Some producers elect to raise food animals without using antibiotics, in what are known as alternative modes of production (see app. II for more information about alternative modes of production).

Antibiotics provide significant benefits to animal production according to USDA. For food animals, the purposes for which FDA approves the use of antibiotics can be divided into the following four categories:

- *Disease treatment:* administered only to animals exhibiting clinical signs of disease.
- *Disease control:* administered to a group of animals when a proportion of the animals in the group exhibit clinical signs of disease.
- *Disease prevention:* administered to a group of animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.
- *Growth promotion*: sometimes referred to as feed efficiency, administered to growing, healthy animals to promote increased weight gain. Such uses are typically administered continuously through the feed or water on a herd- or flock-wide basis. Although such use is not directed at any specifically identified disease, many animal producers believe the use of antibiotics for growth promotion has the additional benefit of preventing disease, and vice versa.

In recent years, both FDA and WHO have sought to identify antibiotics that are used in both animals and people and that are important to treat human infections, also known as medically important antibiotics. Specifically, according to FDA, a medically important antibiotic is given the highest ranking—critically important—if it is used to treat foodborne illness and if it is one of only a few alternatives for treating serious human disease. For example, the fluoroquinolone class of antibiotics is critically important to human medicine because it is used to treat foodborne illnesses caused by the bacteria *Campylobacter* (one of the most common causes of diarrheal illness in the United States), and it is also one of only a few alternatives for treating serious multidrug resistant infections in humans. Some fluoroquinolones are also approved to treat respiratory infections in cattle.

Several Federal Agencies Have Responsibilities and Authorities Related to Animal Antibiotic Use

Two federal departments are primarily responsible for ensuring the safety of the U.S. food supply, including the safe use of antibiotics in food animals—HHS and USDA. Each department contains multiple agencies that contribute to the national effort to assess, measure, and track antibiotic use and resistance (see table 1). Both HHS and USDA officials have stated that it is likely that the use of antibiotics in animal agriculture leads to some cases of antibiotic resistance among humans and that medically important antibiotics should be used judiciously in animals.

Table 1: Agencies with Responsibilities Related to Antibiotics in Food Animals

Department	Agency	Contribution to antibiotic resistance efforts
HHS	Centers for Disease Control and Prevention (CDC)	Conducts surveillance[a] and other research to assess the extent of antibiotic resistance and contributes data about antibiotic resistance in humans to the interagency National Antimicrobial Resistance Monitoring System (NARMS), a national public health surveillance system to track antibiotic resistance in foodborne bacteria. Promotes appropriate use of antibiotics in animals through educational activities and training.
	FDA	Approves for sale and regulates the manufacture and distribution of animal antibiotics. Coordinates NARMS (with CDC and ARS) and contributes data about antibiotic resistance in retail meat. Conducts research on antibiotic resistance and educates animal antibiotic users about appropriate use.
	National Institutes of Health (NIH)	Conducts research on recognizing, responding to, and circumventing the processes that contribute to antibiotic resistance.
USDA	Animal and Plant Health Inspection Service (APHIS)	Manages the National Animal Health Monitoring System (NAHMS)—a periodic, national survey of producers that focuses on animal health, welfare, and production. Manages the National Veterinary Accreditation Program, which certifies private veterinarians to carry out certain federal animal health programs.
	Agricultural Research Service (ARS)	Conducts research in the food safety and animal health programs on alternatives to antibiotics, and the development, persistence, and transmission of antibiotic-resistant organisms or resistance genes. Contributes data about antibiotic resistance in bacteria from food animals at slaughter plants to NARMS.[b]
	Economic Research Service (ERS)	Conducts the Agricultural Resource Management Survey (ARMS), which principally focuses on farm finances, and their links to farm production practices and management decisions. The survey is also used to track and analyze practices, including antibiotic use, as they relate to food safety and the production and availability of food animals.
	Food Safety and Inspection Service (FSIS)	Inspects slaughter plants, food processing, and import establishments in the United States. Contributes samples collected from food animals or food animal products at slaughter plants as a part of NARMS.
	National Institute of Food and Agriculture (NIFA)[c]	Funds research, education, and extension or outreach activities on antibiotic resistance through grants to universities and other organizations.

Source: GAO.

[a]According to the interagency task force, public health surveillance is the ongoing and systematic collection, analysis, and interpretation of data for use in the planning, implementation, and evaluation of public health practice.

[b]ARS also tests bacteria gathered through NAHMS for antibiotic resistance.

[c]NIFA was formerly known as the Cooperative State Research, Education, and Extension Service.

As mentioned, HHS and USDA agencies participate in the Interagency Task Force on Antimicrobial Resistance, which developed a plan in 2001 to help federal agencies coordinate efforts related to antibiotic resistance. The 2001 interagency plan contains 84 action items organized in four focus areas: surveillance, prevention and control, research, and product development. According to the 2001 interagency plan, public health surveillance, which includes monitoring for antibiotic resistance, is the ongoing and systematic collection, analysis, and interpretation of data for use in the planning, implementation, and evaluation of public health practice. Many of the plan's action items focus on antibiotic use and resistance in humans, and some action items address the use of antibiotics in agriculture, including food animal production, and are directly relevant to this report. For example, one action item in the surveillance focus area states the agencies' intentions to develop and implement procedures for monitoring antibiotic use in agriculture, as well as in human medicine. Another states that agencies will expand surveillance for antibiotic-resistant bacteria in sick and healthy food animals on farms and at slaughter plants, as well as in retail meat, such as chicken, beef, and pork. The action plan also contains action items related to research on alternatives to antibiotics and providing education to producers and veterinarians about appropriate antibiotic use.

Since 2001, HHS and USDA have used the interagency task force to coordinate their activities on antibiotic resistance. For example, each year the task force produces an annual report listing activities completed in that year related to the 2001 interagency plan. The task force recently released a 2010 version of the interagency plan, which is still in draft form but is expected to be finalized this year. The draft 2010 interagency plan contains some new initiatives and also reformulates many of the action items listed in the 2001 plan to be more action-oriented.

Pork Production

Source: GAO.

The United States is the world's third-largest pork producer and largest pork exporter. Pigs are produced in several types of specialized operations. Farrow-to-finish operators raise pigs from birth to slaughter. In multisite pig production, different phases of production occur at different locations, and breeding pigs are isolated from other pigs at various stages of production. After weaning, pigs move into either a "wean-to-finish" building, where they stay until sent to slaughter, or to a "nursery" building (pictured above) and, 6-8 weeks later, to a "finisher" building until slaughter. According to USDA, the U.S. pork industry has shifted rapidly toward fewer large operations, and operations that specialize in a single phase of production have replaced many farrow-to-finish operations. According to the National Pork Producers' Council, multisite production is designed to keep pigs of the same age together and maximize pig health. Producers minimize disease exposure by keeping pigs in the same groups and thoroughly cleaning barns between herds. However, moving pigs from site to site also presents disease challenges as pigs are exposed to new bacteria from new environments and other animals. Producers may use antibiotics to prevent diseases during vulnerable periods, as well as to treat illnesses. Pork producers may also use antibiotics for growth promotion, particularly when feed costs are high.

Agency Data Are Limited and Restrict Efforts to Understand Antibiotic Resistance

The 2001 interagency plan discusses two types of data needed to understand antibiotic resistance—data on the amount of antibiotics used in food animals ("use data") and data on the level of antibiotic resistance in bacteria found in food animals and retail meat ("resistance data"). Agencies have collected some data to track antibiotic use in animals, but these data lack crucial details identified by the 2001 interagency plan as essential for agencies to examine trends and understand the relationship between use and resistance. To collect data on antibiotic resistance, agencies have leveraged existing programs, but because these programs were designed for other purposes, their sampling methods do not yield data that are representative of antibiotic resistance in food animals and retail meat across the United States. USDA also collected data on both use and resistance in a pilot program that was discontinued.

Agencies Collect Data on Use That Lack Crucial Details

The 2001 interagency plan set a "top priority" action item of monitoring antibiotic use in veterinary medicine, including monitoring data regarding species and purpose of use. The plan stated this information is essential for interpreting trends and variations in rates of resistance, improving the understanding of the relationship between antibiotic use and resistance, and identifying interventions to prevent and control resistance. The task force's draft 2010 interagency plan reiterates the importance of monitoring antibiotic use and sets a goal to better define, characterize, and measure the impact of antibiotic use in animals.

Three federal efforts collect data about antibiotic use in food animals (see table 2). One of these efforts, run by FDA, was created by Congress as a reporting requirement for pharmaceutical companies to provide sales data. The other two efforts are run by USDA agencies and collect on-farm data on antibiotic use by incorporating questions into existing surveys of food animal producers.

Table 2: Current Federal Efforts Collecting Data on Antibiotic Use

Program	Agency	Information collected	Source of information	Frequency of reporting
Animal Drug User Fee Amendments of 2008	FDA	(1) the amount of each antibiotic sold by container size, strength, and dosage form; (2) quantities distributed domestically and quantities exported; and (3) a listing of the target animals, and the approved ways each antibiotic can be used	New Animal Drug sponsors (generally pharmaceutical companies)	Annual
NAHMS	APHIS	Information about how antibiotics are administered (e.g., in water, feed, or by injection), the number of animals treated, producers' preferred antibiotics for various ailments, and situations when producers would use an antibiotic	Producers	Varies; every 6-7 years for most animal commodities
ARMS	ERS	Information about antibiotic use as a production practice, such as how antibiotic use affects livestock production and farm financial performance	Producers	Varies; approximately every 5 years

Source: GAO.

Sales Data

Since our 2004 report,[5] FDA has begun to collect and publish data from pharmaceutical companies on antibiotics sold for use in food animals, as required by the Animal Drug User Fee Amendments of 2008 (ADUFA). Under ADUFA, the sponsor of an animal antibiotic—generally a pharmaceutical company—must report annually to FDA: (1) the amount of each antibiotic sold by container size, strength, and dosage form; (2) quantities distributed domestically and quantities exported; and (3) a listing of the target animals and the approved ways each antibiotic can be used (called indications). Section 105 of ADUFA also directs FDA to publish annual summaries of these data. To fulfill this requirement, FDA published the first of these reports on its public Web site in December 2010. (See app. III for examples of antibiotic sales data collected by FDA.) However, to protect confidential business information, as required by statute, FDA's report summarizes the sales data by antibiotic class, such as penicillin or tetracycline, rather than by specific drug and also aggregates sales data for antibiotic classes with fewer than three distinct sponsors.

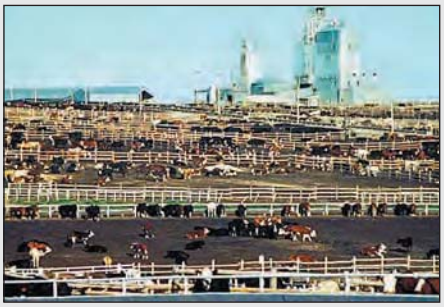
[5]GAO-04-490.

In submitting the original ADUFA legislation for the House of Representatives to consider, the House Committee on Energy and Commerce stated that it expected these data to further FDA's analysis of, among other things, antibiotic resistance, but the data do not include crucial details that would be needed to do so. Specifically, ADUFA does not require FDA to collect information on the species in which antibiotics are used and the purpose of their use. According to representatives of all the producer and public health organizations we spoke with, because FDA's sales data lack information on the species in which the antibiotic is used, these data do not allow the federal government to achieve the antibiotic use monitoring action item in the 2001 interagency plan, including interpreting trends and variations in rates of resistance, improving the understanding of the relationship between antibiotic use and resistance, and identifying interventions to prevent and control resistance. For example, a representative of one public health organization stated that species-specific data is needed to link antibiotic use in animals with resistance in animals and food. Representatives of most of the public health organizations also stated that the government needs to collect data on the purpose of antibiotic use—that is if the antibiotic is being given for disease treatment, disease control, disease prevention, or growth promotion. Furthermore, representatives of some public health organizations indicated that data on antibiotic use should be integrated with information on antibiotic resistance to allow analysis of how antibiotic use affects resistance. However, a representative of an animal pharmaceutical organization stated that FDA should not attempt to collect national-level antibiotic use data and should instead collect local data to facilitate study of farm management practices in order to help farmers better use antibiotics.

According to FDA officials, sales data can provide an overall picture of the volume of antibiotics sold for use in animals. However, FDA faces several challenges in collecting detailed antibiotic sales data from drug sponsors. First, if an antibiotic is approved for use in multiple species, drug sponsors may not be able to determine how much of their product is used in a specific species. Second, if an antibiotic is approved for multiple purposes, drug sponsors also may not be able to determine how much is used for each purpose. Third, antibiotics may be stored in inventory or expire before they are used, so the quantity sold and reported to the FDA may not equal the quantity actually used in animals. FDA officials acknowledged the limitation of their current sales data and noted that the agency is exploring potential approaches to gather more detailed sales data or other information on actual antibiotic use.

On-Farm Data

Beef Production



Source: USDA.

The United States is the world's largest producer of beef. The beef industry is roughly divided into two production sectors: cow-calf operations and cattle feeding. Beef cattle are born in a cow-calf operation, where both cows and calves are fed grass in a pasture year-round. Once weaned, most cattle are sent to feedlots, where they are fed grain for about 140 days. The beef industry has become increasingly concentrated. According to USDA, feedlots with 1,000 or more head of cattle comprise less than 5 percent of total feedlots in the United States, but market 80 to 90 percent of fed cattle. Weaning, shipping, and processing put stress on cattle and compromise their immune systems. According to the National Cattleman's Beef Association, beef producers use antibiotics to treat common illnesses, including respiratory disease, eye infections, intestinal disease, anaplasmosis (a red blood cell parasite), and foot infections. Some cattle producers also use antibiotics for growth promotion.

Two USDA agencies collect data on antibiotic use from food animal producers by incorporating questions into existing surveys. One of these surveys, managed by APHIS, is the National Animal Health Monitoring System (NAHMS), a periodic, national survey of producers that focuses on animal health and management practices. APHIS staff collect information from producers on how antibiotics are administered (e.g., in water, feed, or injection), what antibiotics they prefer for various ailments, and in what situations they would use an antibiotic. To collect this information, APHIS staff visit farms multiple times over the course of 3 to 6 months and survey producers' practices. Previous NAHMS surveys have examined management practices for dairy cows, swine, feedlot cattle, cow-calf operations, small broiler chicken flocks, and egg-laying chicken flocks, among other species. APHIS officials told us that one of NAHMS' strengths is its national scope and that NAHMS can be used to examine changes in animal management practices, including antibiotic use practices, between NAHMS surveys. However, as we reported in 2004, NAHMS produces a snapshot of antibiotic use practices in a particular species, but the data it collects cannot be used to monitor trends in the amount of antibiotics used over time. According to APHIS officials, these limitations remain today. For example, these officials said that NAHMS is limited by long lag times (approximately 6 years) between surveys of the same species, changes in methodology and survey populations between studies, reliance on voluntary participation by food animal producers, and collection of qualitative, rather than quantitative information on antibiotic use.

Since our 2004 report, USDA's ERS has begun to collect information on antibiotic use through the Agricultural Resource Management Survey (ARMS)—a survey of farms conducted since 1996—though these data have limitations similar to those of NAHMS. ERS uses ARMS data to study how production practices, including antibiotic use, affect financial performance and whether specific production practices can substitute for other production practices. For example, a January 2011 ERS study found that broiler chicken producers who forgo subtherapeutic uses of antibiotics (i.e., use in chickens that are not ill) tend to use distinctly different production practices, such as testing flocks and feed for

pathogens, fully cleaning chicken houses between each flock, and feeding chickens exclusively from vegetable sources. However, like NAHMS, ARMS cannot be used to examine trends in antibiotic use over time because ERS does not resurvey the same farms over time or conduct annual surveys on specific commodities.

According to officials from agencies and some organizations, it is challenging to collect detailed data on antibiotic use in animals from producers for a variety of reasons. First, producers may not always maintain records on antibiotic use. Second, producers who do collect these data may be reluctant to provide them to the federal government voluntarily. FDA is exploring its legal options for requiring producers to report antibiotic use data to FDA. In addition, we observed during our site visits that the types of use data producers collected varied widely. For example, one producer used electronic systems to track all treatments by individual animal, whereas others maintained paper records, and one maintained no records. Also, some food animal species, such as broiler chickens, are generally produced by integrated companies, which own the chickens from birth through processing and contract with a grower to raise them. These growers often receive feed as part of a contract and may not know whether that feed contains antibiotics. For example, one grower we visited did not know that his animals received antibiotics for growth promotion, though the veterinarian from his integrated company indicated that they did. Surveys, such as NAHMS and ARMS, that rely on producers or growers to provide antibiotic use data may be particularly limited by this lack of available data. Moreover, collecting data on-farm from producers is expensive for the federal agencies involved due to the large amount of personnel and time required.

Agencies also face challenges collecting antibiotic use data from other sources. For example, use data gathered from veterinarians may be of limited value because, according to FDA officials, many antibiotics can be purchased without veterinary involvement. In cases where antibiotics do require a prescription, the usefulness of records maintained by veterinarians may vary. For example, one veterinary clinic we visited maintained extensive paper records dating back 2 years, but because they were not electronic, these records would be difficult to analyze. In addition, a veterinary organization we spoke with stated that it would be cumbersome for veterinarians to provide this information to an agency because there is no centralized reporting mechanism, such as an electronic database, for them to do so. According to an official from an organization representing the animal feed industry, feed mills also maintain records on antibiotics mixed into animal feed, including the

Poultry Production

Source: USDA.

The United States is the world's largest poultry producer and second-largest poultry exporter, with broiler chickens—those used for meat—comprising over four-fifths of U.S. poultry production. The broiler chicken industry in the United States is vertically integrated, meaning that the same company—the integrator—generally owns the birds from birth through processing. Integrators contract with local, independent growers to raise the birds, providing chicks, feed, and veterinary services to the grower and visiting each facility regularly to check for health issues. (Above is a picture of broiler chickens in a grower facility.) According to the National Chicken Council, broiler producers may use antibiotics to treat diseases, such as bacterial enteritis (which causes diarrhea in chickens), as well as for growth promotion.

amount of antibiotic used and the type of feed the antibiotic went into. Although feed mills do not intentionally track antibiotic use by species, the official said that collectively, this information could be used to track antibiotic use by species. However, FDA officials told us that collecting use data from feed mills would require the development of a new reporting mechanism for these data.

Agencies Are Leveraging Existing Programs to Collect Resistance Data, but These Data Are Not Representative

In 2004, we reported that the federal government collects resistance data through the National Antimicrobial Resistance Monitoring System (NARMS), established in 1996. NARMS is an interagency effort that monitors antibiotic resistance in certain bacteria under three programs: the animal component, led by ARS, samples bacteria from food animals at slaughter plants; the retail meat component, led by FDA, samples retail meat purchased from grocery stores; and the human component, led by CDC, samples bacteria from humans (see table 3). FDA serves as the funding and coordinating agency. From fiscal years 2006 through 2010, the NARMS budget remained constant at $6.7 million, with ARS, FDA, and CDC receiving $1.4 million, $3.5 million, and $1.8 million, respectively. NARMS received a funding increase in fiscal year 2011, to $7.8 million.

Table 3: Components of NARMS

Agency	Source of bacteria	Bacteria tested for antibiotic resistance
ARS and FSIS	Animals at slaughter plants—chicken, turkey, cattle, swine[a]	*Salmonella* (chicken, turkey, cattle, swine) *Campylobacter* (chicken) *E. coli* (chicken) *Enterococcus* (chicken)
FDA	Retail meat—samples of chicken breasts, pork chops, ground turkey, ground beef	All 11 participating states[b] culture four products for *Salmonella* and two products (chicken breast and ground turkey) for *Campylobacter*. 4 of these states also culture four products for *E. coli* and *Enterococcus*.
CDC	Humans	All 50 states culture for typhoidal *Salmonella*, non-typhoidal *Salmonella*, *E. coli* O157, *Shigella* 10 states culture *Campylobacter*[c]

Source: GAO.

[a]ARS also tests bacteria gathered through NAHMS for antibiotic resistance.

[b]FoodNet is a collaborative project between CDC and 10 participating states: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee.

[c]In addition, some states culture non-clinical *Enterococcus* and *E. coli*. CDC also previously tested *Listeria* and generic *E. coli*, but is not currently doing so.

The 2001 interagency plan contains an action item stating agencies will design and implement a national antibiotic resistance surveillance plan. Among other things, the 2001 interagency plan states that agencies will expand and enhance coordination of surveillance for drug-resistant bacteria in sick and healthy animals on farms, food animals at slaughter plants, and retail meat. The plan also states that collecting data on antibiotic resistance will help agencies detect resistance trends and improve their understanding of the relationship between use and resistance. The draft 2010 interagency plan also reiterates the importance of resistance surveillance and includes several action items aimed at strengthening, expanding, and coordinating surveillance systems for antibiotic resistance. According to WHO's *Surveillance Standards for Antimicrobial Resistance*, which provides a framework to review existing antibiotic resistance surveillance efforts, populations sampled for surveillance purposes should normally be representative of the total population—in this case, food animals and retail meat in the United States. Additionally, WHO's surveillance standards state that it is important to understand the relationship of the population surveyed to the wider population, meaning that agencies should understand how food animals and retail meat surveyed in NARMS are similar to food animals and retail meat throughout the United States.

The food animal component of NARMS, led by ARS, gathers bacteria from food animal carcasses at slaughter plants and tests them for antibiotic resistance, but because of a change in sampling method has become less representative of food animals across the United States since we reported in 2004. ARS receives these samples from an FSIS regulatory program called the Hazard Analysis and Critical Control Points (HACCP) verification testing program, which is designed to, among other things, reduce the incidence of foodborne illness. FSIS inspectors work in slaughter plants around the country, where they collect samples from carcasses to test for foodborne pathogens, among other duties. When we last reported on antibiotic resistance in 2004, HACCP verification testing included two sampling programs—a nontargeted program, in which inspectors sampled randomly selected plants, and a targeted program, in which slaughter plants with a higher prevalence of bacteria causing foodborne illness were more likely to be selected for additional sampling. In 2006, FSIS eliminated the random sampling program, which FSIS officials told us has allowed the agency to use its resources more effectively. FSIS now conducts only targeted sampling of food animals in its HACCP verification testing. This nonrandom sampling method means the NARMS data obtained through HACCP are not representative of food animals across the country and cannot be used for trend analysis because bacteria tested by NARMS are now collected at greater rates from slaughter plants that are not in compliance with food safety standards. According to FDA officials, due to this sampling method, the resulting data are skewed for NARMS purposes.

The NARMS retail meat component, led by FDA, collects samples of meat sold in grocery stores and tests them for antibiotic-resistant bacteria, but these samples may not be representative of retail meat throughout the United States. The program began in 2002 and has since expanded to collect retail meat samples from 11 states: the 10 participant states in CDC's FoodNet program, which conducts surveillance for foodborne diseases, plus Pennsylvania, which volunteered to participate in retail meat sampling (See table 3 for the types of bacteria tested). Due to its nonrandom selection of states, FDA cannot determine the extent to which NARMS retail meat samples are representative of the United States. FDA collects bacteria from those states that volunteer to participate in the program, so some regions of the country are not represented in the NARMS retail meat program. According to the FDA Science Advisory Board's 2007 review of NARMS, this lack of a national

sampling strategy limits a broader interpretation of NARMS data.[6] According to FDA officials, FDA has not analyzed how representative these samples are of the national retail meat supply in the United States but officials believe that the samples provide useful data that serves as an indicator for monitoring US retail meat.

FDA is aware of the sampling limitations in NARMS and has articulated a strategic goal of making NARMS sampling more representative and applicable to trend analysis in a draft 2011-2015 NARMS Strategic Plan, which was released for public comment in January 2011. The comment period closed in May 2011, and FDA is currently making changes to the plan based on the submitted comments. The plan states that NARMS will become more representative by, among other things, modifying its animal sampling to overcome the biases resulting from the current reliance on HACCP verification testing and improving the geographic representation of retail meat testing, though FDA has not yet planned specific actions to achieve this goal.

According to FDA officials, in light of increased funding for NARMS in 2011, they are exploring ways to improve NARMS sampling to make it more representative. FDA hosted a public meeting in July 2011 to solicit public comment on NARMS animal and retail meat sampling improvements. At this meeting, ARS officials discussed two new on-farm projects—one pilot project, in collaboration with FDA, plans to collect samples from feedlot cattle, dairy cows, and poultry with the goal of evaluating potential sampling sites within the food animal production chain (e.g., on farms or in holding pens at slaughter plants). The second project is in collaboration with Ohio State University and plans to use industry personnel to collect samples from poultry and swine producers. Both projects will test samples for antibiotic resistance through NARMS. Some of the additional suggestions discussed during this meeting included changing FSIS sampling to provide more representative data to NARMS, discontinuing slaughter plant sampling altogether in favor of an on-farm sampling program, and increasing the number of state participants in the retail meat sampling program.

[6]FDA Science Advisory Board, *National Antimicrobial Resistance Monitoring System (NARMS) Program Review* (May 25, 2007).

The NARMS human component, led by CDC, collects and tests bacteria from health departments in all 50 states and the District of Columbia. We reviewed the issue of antibiotic resistance and antibiotic use in humans in 2011. This review examined, among other things, the human component of NARMS and concluded that CDC's data is nationally-representative for four of the five bacteria included in the program.[7]

In our interviews, representatives of producer and public health organizations identified several challenges associated with collecting data on antibiotic resistance. First, according to representatives from most public health organizations, ARS, FDA, and CDC are limited by available funding. Sampling and testing bacteria can be expensive, and agencies have to balance competing priorities when allocating resources. For example, in the NARMS retail meat program, FDA could choose to expand retail meat sampling geographically by adding new states to the program, expand the number of bacteria tested, expand the number of samples collected, or expand the types of meat sampled. Second, according to representatives of several producer and public health organizations, agencies may face challenges cooperating and reaching consensus with one another. For example, NARMS reports do not include interpretation of resistance trends across NARMS components. Specifically, while NARMS issues annual Executive Reports that combine data from all three components of NARMS (available on FDA's Web site), these reports do not provide interpretation of NARMS data. According to FDA officials, it is difficult to develop consensus on interpretation for these reports because agencies differ in their interpretations and preferred presentations of NARMS data. Third, according to the FDA Science Advisory Board's 2007 review of NARMS, the lag between NARMS data collection and report issuance can sometimes be excessive. For example, as of August 2011, the latest NARMS Executive Report covered 2008 data. According to FDA and CDC officials, the process of testing bacteria, analyzing and compiling data, and obtaining approval from agencies is time-consuming and increases the lag time of NARMS reports.

In our interviews, representatives of public health organizations also suggested that federal agencies collect additional types of resistance data. First, representatives of several organizations suggested that

[7]For more information, see GAO, *Antibiotic Resistance: Data Gaps Will Remain Despite HHS Taking Steps to Improve Monitoring*, GAO-11-406 (Washington, D.C.: June 1, 2011).

agencies expand the types of bacteria tested for antibiotic resistance. FDA is aware of this suggestion and has considered whether to add to the types of bacteria it tests. For example, recent studies have discussed methicillin-resistant *Staphylococcus aureus* (MRSA) in retail meat. MRSA is a type of bacteria that is resistant to several antibiotics, including penicillin, and that can cause skin infections in humans and more severe infections in health care settings. In response, FDA is conducting a pilot study to collect data on the prevalence of MRSA in retail meat. However, according to FDA officials, FDA is unlikely to include MRSA in its regular NARMS testing because general consensus in the scientific community is that food does not transmit community-acquired MRSA infections in humans. Second, representatives of three public health organizations suggested that federal agencies link resistance data with data on outbreaks of foodborne illness in humans, which representatives of one organization stated could help scientists document the link between animal antibiotic use and resistant outbreaks of foodborne illness. According to representatives of this organization, NARMS' resistance data are not currently linked to information about foodborne disease outbreaks. According to CDC officials, CDC tests bacteria associated with foodborne illness outbreaks in humans for antibiotic resistance, but does not routinely publish these data.

USDA Discontinued a Program That Collected Data on Both Use and Resistance

When we last reported on antibiotic resistance in 2004, APHIS, ARS, and FSIS collected on-farm use and resistance data from 40 swine producers through the pilot Collaboration in Animal Health and Food Safety Epidemiology (CAHFSE), but this program faced challenges in collecting data and was discontinued in 2006 due to lack of funding. By collecting information from the same facilities over time, agencies could use CAHFSE data to examine the relationship between antibiotic use and resistance. However, according to officials at APHIS and ARS, collecting quarterly on-farm data was burdensome and generated a large number of bacterial samples, which were costly to test and store. Although the agencies wanted to use CAHFSE to monitor antibiotic resistance throughout the food production system, officials from all three agencies told us that this "farm to fork" monitoring raised logistical challenges. For example, FSIS officials examined the feasibility of monitoring resistance data through the slaughter plant but discovered that slaughter plants were reluctant to participate in the program due to fear of enforcement actions and confidentiality concerns. According to APHIS officials, CAHFSE released quarterly and annual data summaries, but it did not issue an overall capping report or formal evaluation of the program.

CAHFSE was discontinued, but NAHMS continues to collect three types of bacteria (*Salmonella*, *Campylobacter*, and *E. coli*) from a subset of surveyed producers and sends them to ARS for antibiotic resistance testing. However, as discussed earlier in this report, NAHMS data provide a snapshot of a particular species but cannot be used to monitor trends. Additionally, as discussed earlier in this report, ARS has started two on-farm projects to collect bacteria from food animals. In one of these projects, which collects samples from poultry and swine, ARS partners with integrated companies to collect a variety of samples from producers. According to an ARS official, because personnel to collect samples were responsible for the majority of costs in the CAHFSE program, using industry personnel rather than ARS staff to collect on-farm samples can significantly reduce the costs of on-farm sampling.

Although data on both use and resistance can be difficult to collect, other countries have been successful in doing so. For example, the Canadian government's Canadian Integrated Program on Antimicrobial Resistance Surveillance (CIPARS), created in 2002, provides an example of on-farm collection of antibiotic use and resistance data. In addition to gathering resistance data similar to NARMS, CIPARS also has an on-farm component, which collects antibiotic use information annually from about 100 swine producers and integrates it with data from resistance testing on fecal samples from the same farms. CIPARS addresses funding limitations by restricting on-farm surveillance to swine, sampling annually rather than quarterly, and collecting slaughter plant samples through industry personnel. A CIPARS official stated that the program's on-farm data could be used to link antibiotic use and antibiotic resistance at the herd level and help identify interventions to prevent antibiotic resistance. CIPARS issues annual reports, which include interpretation of the data such as discussions of trends over time. For example, the most recent report, from 2007, noted an increase in the percentage of bacteria resistant to several antibiotics in samples collected from pigs at slaughter plants from 2003 to 2007.

Denmark also has a use and resistance data collection system, called the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP). Data collection covers antibiotic use in food animals and humans, as well as antibiotic resistance in food animals, meat in slaughter plants and at retail, and in humans. The objectives of DANMAP are to monitor antibiotic use in food animals and humans; monitor antibiotic resistance in bacteria from food animals, food of animal origin, and humans; study associations between antibiotic use and resistance; and identify routes of transmission and areas for further research studies.

According to DANMAP officials, Denmark achieves these goals by gathering data on veterinary prescriptions, since all antibiotic use in Denmark is via prescription-only. For veterinary prescriptions, these officials told us Denmark gathers data on the medicine being prescribed, the intended species and age group in which the prescription will be used, the prescribed dose of the antibiotic, the prescribing veterinarian, and the farm on which the prescription will be used. Further, DANMAP collects information on antibiotic resistance in food animals, from healthy animals at slaughter plants and from diagnostic laboratory submissions from sick animals. Denmark also gathers both domestically produced and imported retail meat samples from throughout the country to test for antibiotic resistance. DANMAP officials noted that, in Denmark, the industry is responsible for collecting and submitting bacterial samples from slaughter plants for testing, according to a voluntary agreement, and that the industry spends additional funds to do so. DANMAP issues annual reports, which include interpretation of data on antibiotic use in animals and humans, as well as data on antibiotic resistance in bacteria from food animals, retail meat, and humans. Some DANMAP reports also include more detailed analysis of particular areas of interest. For example, the 2009 DANMAP report examined *E. coli* resistant to penicillins in pigs, retail meat, and humans and found that antibiotic use in both animals and humans contributes to the development of penicillin-resistant *E. Coli*. See appendix IV for more information on DANMAP.

FDA Implemented a Process to Mitigate Resistance Risk for Newer Antibiotics but Faces Challenges with Older Antibiotics

FDA implemented a risk assessment process for antibiotic sponsors, generally pharmaceutical companies, to mitigate the risk of resistance in food animals to antibiotics approved since 2003. However, the majority of antibiotics used in food animals were approved prior to 2003, and FDA faces significant resource challenges in assessing and mitigating the risk of older antibiotics. Instead, FDA has proposed a voluntary strategy to mitigate this risk but has neither developed a plan nor collected the "purpose of use" data necessary to measure the effectiveness of its strategy.

FDA Implemented a Risk Assessment Process to Mitigate Resistance Risk for New Antibiotics

FDA approves for sale, and regulates the manufacture and distribution of, drugs used in veterinary medicine, including drugs given to food animals. Prior to approving a new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal. It must also determine that the new drug intended for animals is safe with regard to human health, meaning that there is reasonable certainty of no harm to human health from the proposed use of the drug in animals. FDA

may also take action to withdraw an animal drug when new evidence shows that it is not safe with regard to human health under the approved conditions of use.

In 2003, FDA issued guidance recommending that antibiotic sponsors include a risk assessment of any new antibiotics for use in food animals. The guidance is known as *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*, Guidance for Industry #152. Under this framework, an antibiotic sponsor would assess three factors: the probability that the resistant bacteria are present in the animal as a consequence of the antibiotic use, the probability that humans would ingest the bacteria in question, and the probability that human exposure to resistant bacteria would result in an adverse health consequence. As part of the third factor, the sponsor considers the importance of the antibiotic to treating human illness, under the assumption that the consequences of resistance are more serious for more important antibiotics. The guidance provides a preliminary ranking of antibiotics considered medically important to human medicine, with the highest ranking assigned to antibiotics deemed "critically important" if it is (1) used to treat foodborne illness and (2) one of only a few alternatives for treating serious human disease. An antibiotic is considered highly important if it meets one of these two criteria. By considering all three factors, the sponsor estimates the overall risk of the antibiotic's use in food animals adversely affecting human health. Though this risk assessment process is recommended by FDA, the antibiotic sponsor is free to prove the safety of a drug in other ways and to consult with FDA to decide if the approach is recommended for its animal antibiotic application. FDA officials said that, in practice, the risk of antibiotic resistance is considered as part of any new animal antibiotic approval.

According to FDA documents, this risk assessment process has been effective at mitigating the risk of resistance posed by new antibiotics because antibiotic sponsors usually consider the risk assessment process in their product development, so the products ultimately submitted for approval are intended to minimize resistance development. Representatives of some producer, public health, and veterinary organizations, as well as an animal pharmaceutical organization, told us that they were generally satisfied with the risk assessment approach. For example, a representative of an animal pharmaceutical organization commented that the risk assessment process was helpful in that it provided a clear road map for drug approvals. Representatives of a veterinary organization said they were pleased that new antibiotics were

examined using a comprehensive, evidence-based approach to risk assessment.

However, several organizations also raised concerns. For instance, a representative of an animal pharmaceutical organization said that FDA's risk assessment process was an overly protective "blunt instrument," since FDA would likely not approve any antibiotic product designed for use in feed to prevent or control disease in a herd or flock if the antibiotic is critically important to human health. Representatives from this pharmaceutical organization and a veterinary organization said that FDA's guidance makes it very difficult for antibiotic sponsors to gain approval for new antibiotics for use in feed or water.

In addition, representatives of several public health organizations said that flaws in the criteria FDA used to rank medically important antibiotics may lead the agency to the inappropriate approval of animal antibiotics. For example, they identified a class of antibiotics known as fourth-generation cephalosporins, which are an important treatment for pneumonia in humans and one of the sole therapies for cancer patients with certain complications from chemotherapy. However, since neither of these are also foodborne diseases, under FDA criteria this antibiotic is not ranked as critically important in treating human illness, which these organizations said could lead to the approval of fourth-generation cephalosporins for use in food animals and, eventually, increased antibiotic resistance. FDA officials recently said they intend to revisit the antibiotic rankings to reflect current information. However, FDA officials noted that they believed the current ranking appropriately focused on antibiotics used to treat foodborne illnesses in humans given that the objective of the guidance was to examine the risk of antibiotic use in food animals.

FDA Faces Resource Challenges in Assessing the Risk of Older Antibiotics

According to FDA officials, the majority of antibiotics used in food animals were approved prior to 2003. FDA faces significant challenges to withdraw agency approval, either in whole or in part, of these antibiotics if concerns arise about the safety of an antibiotic. If FDA initiates a withdrawal action because of safety questions that have arisen after an antibiotic's approval, the agency has the initial burden of producing evidence sufficient to raise serious questions about the safety of the drug. Once FDA meets this initial burden of proof, the legal burden then shifts to the antibiotic sponsor to demonstrate the safety of the drug. If, after a hearing, the FDA Commissioner finds, based on the evidence produced,

that the antibiotic has not been shown to be safe, then the product approval can be withdrawn.

FDA's 5-year effort to withdraw approval for one antibiotic for use in poultry illustrates the resource-intensive nature of meeting the legal burden to withdraw an approved antibiotic. It is the only example of FDA withdrawing an antibiotic's approval for use in food animals because of concerns about resistance. Specifically, Enrofloxacin, approved in October 1996, is in the critically important fluoroquinolone class of antibiotics, used to treat foodborne illnesses caused by the bacteria *Campylobacter*, and it was used in poultry flocks via the water supply to control mortality associated with *E. coli* and other organisms. In October 2000, based on evidence of increased fluoroquinolone resistance in bacteria from animals and humans, FDA initiated a proceeding to withdraw its approval for the use of two types of fluoroquinolones in poultry. One pharmaceutical company voluntarily discontinued production, but the manufacturer of enrofloxacin challenged the decision. FDA officials told us that it took significant time and resources to gather evidence for the case, even though they had good data showing a correlation between the drug's approval for use in poultry and increasing resistance rates in humans. After an administrative law judge found that enrofloxacin was not shown to be safe for use in poultry as previously approved, the FDA's Commissioner issued the final order withdrawing approval for its use effective September 2005.

FDA officials said that from this case they learned that taking a case-by-case approach to withdrawing antibiotics due to concerns over resistance was time-consuming and challenging. In our 2004 review of federal efforts to address antibiotic resistance risk, we reported FDA was planning to conduct similar risk assessments of other previously approved antibiotics.[8] FDA officials estimated, however, that the enrofloxacin withdrawal cost FDA approximately $3.3 million, which they said was significant. FDA officials told us that conducting individual postapproval risk assessments for all of the antibiotics approved prior to 2003 would be prohibitively resource intensive, and that pursuing this approach could further delay progress on the issue.

[8]GAO-04-490.

FDA Proposed a Voluntary Strategy for Older Antibiotics but Has No Plan to Assess Effectiveness

Instead of conducting risk assessments for individual antibiotics approved prior to 2003, FDA in June 2010 proposed a strategy to promote the "judicious use" of antibiotics in food animals. FDA proposed the strategy in draft guidance titled *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*, draft Guidance for Industry #209. FDA describes judicious uses as those appropriate and necessary to maintain the health of the food animal. The draft guidance includes two principles aimed at ensuring the judicious use of medically important antibiotics. First, that antibiotic use is limited to uses necessary for assuring animal health—such as to prevent, control, and treat diseases. Second, that animal antibiotic use is undertaken with increased veterinary oversight or consultation. To implement the first principle, FDA is working with antibiotic sponsors to voluntarily phase out growth promotion uses of their antibiotics. FDA officials told us they have met with four of the approximately nine major antibiotic sponsors to discuss withdrawing growth promotion uses from their antibiotics' labels and that they plan to engage with generic antibiotic manufacturers in the near future. To implement the second principle of increasing veterinarian oversight of antibiotic use, FDA officials told us that they would like to work with antibiotic sponsors to voluntarily change the availability of medically important antibiotics currently approved for use in feed from over the counter to veterinary feed directive (VFD) status. The majority of in-feed antibiotics are currently available over the counter, but VFD status would instead require these antibiotics to be used with the professional supervision of a licensed veterinarian. In March 2010, FDA issued an advance notice of proposed rulemaking announcing its intention to identify possible changes to improve its current rule on VFDs and seeking public comments on how to do so. FDA officials told us that they received approximately 80 comments by the end of the comment period in August 2010 from interested parties on how to improve the VFD rule, and were taking them into consideration as they drafted the rule, which they hope to publish in 2011. In April 2011, the American Veterinary Medicine Association also formed a new committee to help FDA develop practical means to increase veterinary oversight of antibiotic use.

Representatives of several producer organizations, veterinary organizations, and an animal pharmaceutical organization expressed concern that FDA's focus on ending growth promotion uses would adversely affect animal health. In particular, these representatives said that some animal antibiotics approved for growth promotion may also prevent disease, though they are not currently approved for that purpose. FDA officials said that, in cases where pharmaceutical companies can prove such claims, FDA would be willing to approve these antibiotics for

disease prevention. FDA officials emphasized, however, that they do not want companies to relabel existing growth promotion antibiotics with new disease prevention claims with no substantive change in the way antibiotics are actually used on the farm. FDA officials told us they plan to issue additional guidance for antibiotic sponsors to outline a specific process for making changes in product labels.

Furthermore, representatives of several producer and veterinary organizations we spoke with expressed concerns about FDA's efforts to increase veterinary oversight because there is shortage of large animal veterinarians. As we reported in February 2009, there is a growing shortage of veterinarians nationwide, particularly of veterinarians who care for food animals, serve in rural communities, and have training in public health.[9] Additionally, representatives of veterinary organizations said that the paperwork requirements under VFDs are onerous. In particular, this is because VFDs require the veterinarian to deliver a copy of the VFD to the feed producer directly for each VFD, and there are not yet many systems for electronic distribution.

In addition, representatives of several public health organizations expressed concern that FDA's strategy will not change how antibiotics are used for two reasons. First, because FDA is depending on voluntary cooperation to remove growth promotion uses from antibiotic labels, there is no guarantee that pharmaceutical companies will voluntarily agree to relabel their antibiotics. To underline the seriousness of their concerns, in May 2011, several public health organizations filed a suit to force FDA to withdraw its approval for the growth promotion uses of two antibiotic classes (penicillins and tetracyclines). Second, representatives of some public health organizations noted that several medically important antibiotics (six out of eight) currently approved by FDA for growth promotion or feed efficiency are already approved for disease prevention uses in some species (see table 4), which could negate the impact of FDA's strategy. Because disease prevention dosages often overlap with growth promotion dosages, representatives of one of these organizations said that food animal producers might simply alter the purpose for which the antibiotics are used without altering their behavior on the farm. One veterinarian told us that if FDA withdrew an antibiotic's approval for

[9]GAO, *Veterinarian Workforce: Actions are Needed to Ensure Sufficient Capacity for Protecting Public and Animal Health,* GAO-09-178 (Washington, D.C.: Feb. 4, 2009).

growth promotion, he could continue to give the antibiotic to the animals under his care at higher doses for prevention of a disease commonly found in this species. The veterinarian stated that there is an incentive to do so because using an animal antibiotic can help the producers he serves use less feed, resulting in cost savings. For example, the in-feed antibiotic may cost approximately $1 per ton of feed, but it can save $2 to $3 per ton of feed, making it an effective choice for the producer.

Table 4: The Overlap between Growth Promotion and Disease Prevention Uses in Food Animal Antibiotics

			Approved uses by animal		
Antibiotic class	**FDA ranking of the importance of antibiotic class to human medicine**	**Antibiotic name**	**Cattle**	**Poultry**	**Swine**
Macrolides	Critically important	Tylosin		X	X
		Erythromycin	X	X	X
Lincosamides	Highly important	Lincomycin		X	X
Penicillin	Highly important	Penicillin G Procaine		X	X
Streptogramins	Highly important	Virginiamycin	X	X	X
Tetracyclines	Highly important	Chlortetracycline	X	X	X
		Oxytetracycline	X	X	X
Pleuromutilins	Highly important	Tiamulin			X
Glycolipids	Not ranked	Bambermycins	X	X	X
Polypeptides	Not ranked	Bacitracin	X	X	X
Quinoxalines	Not ranked	Carbadox			X
Ionophores	Not ranked	Monensin	X	X	
		Lasalocid	X	X	
		Laidlomycin	X		

Source: GAO analysis of FDA data.

Note: An “X” indicates FDA approved growth promotion uses, including weight gain and improving feed efficiency. Light gray shading denotes the overlap between antibiotics approved for growth promotion and disease prevention purposes. Boxes in dark gray denote antibiotics not ranked important to human health by FDA.

Although representatives of some producer and public health organizations have raised doubts about the effectiveness of FDA’s strategy, FDA does not have a plan to collect the data necessary to understand the purpose for which antibiotics are being used or have a plan to measure the effectiveness of its strategy to encourage more judicious use of antibiotics in animals. FDA officials told us the agency will consider this strategy to be successful when all the growth promotion uses of medically important antibiotics are phased out. FDA officials were

unable to provide a timeline for phasing out growth promotion uses, though they identified several next steps FDA intends to take, such as finalizing the guidance document describing their voluntary strategy and issuing additional guidance on its implementation, as well as proceeding forward with the VFD rulemaking process. However, FDA officials stated that the agency had no further plans to measure its progress. In addition, FDA will still allow medically important antibiotics to be used for disease prevention. However, because agency data on sales of antibiotics used in food animals do not include the purpose for which the antibiotics are used, it will be difficult for FDA to evaluate whether its strategy has increased the judicious use of antibiotics or simply encouraged a shift in the purpose of use—for instance, from growth promotion to disease prevention—without lessening use. FDA officials told us the agency is exploring approaches for obtaining additional information related to antimicrobial drug use to enhance the antibiotic sales data that is currently reported to FDA as required by ADUFA, but did not provide a timeline for these efforts.

Agencies Took Steps to Research Alternatives and Educate Users, but Progress Is Unclear

USDA and HHS agencies have taken some steps to research alternatives to current antibiotic use practices and educate producers and veterinarians on appropriate use of antibiotics but the extent of these steps is unclear because neither USDA nor HHS has assessed the progress toward fulfilling the related action items in the 2001 interagency plan.

USDA and HHS Have Conducted Research on Alternatives but Have Not Assessed Progress

An action item in the 2001 interagency plan states that federal agencies will promote the development of alternatives to current antibiotic use, including through research. According to the 2001 interagency plan, such alternatives could include researching vaccines and management practices that prevent illnesses or reduce the need for antibiotic use. However, USDA has not tracked its activities in this area, and neither USDA nor HHS has determined progress made toward this action item.

Since 2001, USDA agencies have undertaken some research related to developing alternatives. However, according to agency officials they are unable to provide a complete list of these activities because USDA's research database is not set up to track research at this level of detail. Instead, research is categorized within the larger food safety research portfolio. In addition, the agencies did not report any activities under this action item in the annual reports published by the interagency task force.

Based on documents provided by USDA and research activities that USDA reported to the interagency task force under other research action items, we identified 22 projects the department funded since 2001 related to alternatives to current antibiotic use practices, with total funding of at least $10 million (see app. V). In addition, ARS officials emphasized that the majority of research performed at ARS related to improving agricultural practices can result in reduced antibiotic needs by producers. Officials from both NIFA and ARS said that they had not assessed the extent to which the research conducted helped achieve the action item in the 2001 interagency plan. Indeed, conducting such an assessment would be difficult without a complete list of relevant research activities. NIFA officials told us that additional funding and resources would be needed to conduct such an assessment, but they did not provide more specific details on how many additional resources would be needed to do so. Although an assessment of research activities on alternatives has not been conducted, ARS officials nevertheless said the agency plans to conduct more research on alternatives to antibiotics in the next 5 years.

Similar to USDA agencies, HHS agencies have conducted some research on alternatives. Specifically, from 2001 through 2005, CDC and FDA sponsored at least five research grants that included funding to research alternatives and reduce resistant bacteria in food animals (see app. VI). NIH has conducted research related to antibiotic resistance that may have applications in both humans and in animals, but agency officials told us that NIH considers human health issues its research priority. Like USDA agencies, HHS agencies did not report any research activities under the action item related to antibiotic alternatives to the interagency task force. No HHS agency has sponsored any such research activities since 2005. HHS officials told us this is because USDA may be the most appropriate lead agency for undertaking alternatives research related to food animals. USDA officials acknowledged that they have a role in researching alternatives to antibiotics, although they said that it is also important for HHS to be involved since FDA would likely be the regulatory agency to approve any products resulting from such research. CDC and FDA officials told us that their agencies have not performed any assessments to determine whether their research activities have helped the agency to fulfill this action item in the 2001 interagency plan.

Representatives of the national veterinary, producer, public health, and animal pharmaceutical organizations that we spoke with told us that greater federal efforts are needed to research alternatives to current antibiotic use in animals. In addition, representatives from most of the veterinary and several public health organizations we spoke with said that

the federal government should make greater efforts to coordinate with the food animal industry about researching alternatives to current antibiotic use. Specifically, most representatives from the producer and veterinary organizations emphasized a need for the federal government to provide funding and other resources to the food animal industry for research projects looking at alternatives. For example, representatives from one veterinary organization told us that several national producer and veterinary organizations have goals of utilizing prevention as an alternative to antibiotic use and said that the federal government could help by conducting research on preventive measures such as vaccine development.

The draft 2010 interagency plan includes an action item reiterating that agencies will conduct research on alternatives to current antibiotic use practices, yet USDA and HHS agencies have not evaluated their previous research to determine the extent to which the action item in the 2001 interagency plan was achieved. Without an assessment of past research efforts, agencies may be limited in their ability to identify gaps where additional research is needed. In addition, the draft 2010 interagency plan does not identify steps agencies intend to take to conduct research on alternatives or time frames for taking these steps. In contrast, other action items listed in the draft 2010 interagency plan under the surveillance, prevention and control, and product development focus areas include specific implementation steps illustrating how agencies plan to achieve them. CDC officials told us that the interagency task force agreed not to identify implementation steps until after the final version of the 2010 interagency plan is published, at which time the task force will publish its plans for updating the 2010 interagency plan. In addition, ARS officials said that the interagency task force requested agencies to identify implementation steps that could be accomplished within the next 2 years, and USDA was unable to determine such steps for alternatives research. We have previously reported that evaluating performance allows organizations to track the progress they are making toward their goals, and it gives managers critical information on which to base decisions for improving their programs.[10] Tracking progress and making sound decisions is particularly important in light of the fiscal pressures currently facing the federal government.

[10]GAO, *Executive Guide: Effectively Implementing the Government Performance and Results Act*, GAO/GGD-96-118 (Washington, D.C.: June 1996).

HHS and USDA Educated Users on Appropriate Use but Have Not Assessed Progress

An action item in the 2001 interagency plan states that federal agencies will educate producers and veterinarians about appropriate antibiotic use. Programs at both HHS and USDA have sought to educate users about appropriate antibiotic use, but the impact of these efforts has not been assessed. In addition, agricultural extension agents and national associations also advise producers on appropriate antibiotic use. The draft 2010 interagency plan no longer has an explicit action item related to appropriate antibiotic use education. There is currently one education activity on appropriate antibiotic use, and after the completion of this effort, there are no plans to develop new education activities.

HHS

HHS agencies sponsored six programs to educate producers and veterinarians about appropriate antibiotic use, the last of which ended in 2010 (see table 5). For example, from 2001 through 2010 CDC funded "Get Smart: Know When Antibiotics Work on the Farm"—also called Get Smart on the Farm—an outreach program that sponsored state-based producer education activities to promote appropriate antibiotic use. CDC officials told us that this was one of the first major education efforts to bring together stakeholders from the public health, veterinary, and agricultural communities to discuss the issue of appropriate antibiotic use. Through the Get Smart on the Farm program, CDC hosted three national animal health conferences designed to foster partnerships between these stakeholders. These conferences included discussions of antibiotic use and resistance in animals. Get Smart on the Farm also funded the development of an online curriculum for veterinary students on antibiotic resistance and appropriate use, which became available in December 2010. CDC officials told us that the agency is planning to take an advisory rather than leadership role in future appropriate use education efforts because they believe that FDA and USDA are the appropriate agencies for leading such efforts. CDC reported that it spent approximately $1.7 million on Get Smart on the Farm activities from 2003 through 2010. Both CDC and FDA officials said that the impact of their education activities had not been assessed. HHS officials also said that they currently do not have plans to develop new activities in the future.

a e ducation cti itie e ated to ro riate nti iotic e fro

ency	rantee if a ica e	Pro ect tit e	Pro ect year	De cri tion of t e ro ect
FDA, CDC, NIH	Not applicable	Consumer Education and Outreach Program	00 - 010	National Foundation for Infectious Diseases Annual Conference on Antimicrobial esistance, which included a public comment meeting on the 001 interagency plan each year on the last day of the conference.
FDA, CDC	American eterinary Medical Association	eterinarian Education and Outreach	00 - 006	Four species-specific booklets that explain appropriate antibiotic use principles were published and distributed to veterinarians two videos on appropriate use were also produced for veterinary schools.
CDC	11 states: CO, GA, IA, MI, MN, NE, OH, PA, SC, TN, WA	Get Smart on the Farm: State and Producer Outreach	001- 010	Sponsored three national animal health conferences where antibiotic resistance and use issues were discussed and funded and developed state-based educational programs to promote appropriate antibiotic use.
	Michigan State University and University of Minnesota	Get Smart on the Farm: Antimicrobial esistance earning Site	001- 010	An online curriculum with pharmacology, microbiology, public health, and species-specific modules.
CDC, FDA, APHIS, FSIS, NIFA	Not applicable	American eterinary Medical Association Steering Committee on Antimicrobial esistance	001- 005	Species-specific antibiotic udicious use principles were developed and published for veterinarians and producers.
FDA, USDA	University of California-Davis	Producer Education Program	00 - 005	Sponsored university-based program that educated producers on antibiotic resistance issues education materials were distributed to producers by Web-based programs and CD- OM.

Source: GAO analysis of agency data.

USDA

USDA agencies also sponsored education programs addressing appropriate antibiotic use in animals (see table 6). For example, from 00 through 005, USDA agencies worked with FDA to fund university-based programs that sought to educate producers on animal health issues, including antibiotic resistance. From 006 through 010 USDA agencies did not report any activities under this action item in the annual reports published by the interagency task force. However, officials noted that education on appropriate antibiotic use remains a priority and that during these years USDA gave presentations at scientific meetings and universities on this topic. USDA officials said the impact of these education efforts was not assessed.

Table 6: USDA Education Activities Related to Appropriate Antibiotic Use from 2001-2011

Agency(s)	Grantee(s) (if applicable)	Project title	Project year(s)	Description of the project
APHIS	Iowa State University	Antibiotic Resistance Continuing Education Learning Module	2011-2012	1 of 19 modules that veterinarians may complete in order to maintain their National Veterinary Accreditation Program accreditation. Expected to be complete and fully integrated into the accreditation program by June 2012.
CDC, FDA, APHIS, FSIS, NIFA	Not applicable	American Veterinary Medical Association Steering Committee on Antimicrobial Resistance	2001-2005	Species-specific antibiotic judicious use principles were developed and published for veterinarians and producers.
FDA, USDA	University of California-Davis	Producer Education Program	2002-2005	Sponsored university-based program that educated producers on antibiotic resistance issues; education materials were distributed to producers by web-based programs and CD-ROM.

Source: GAO analysis of agency data.

The one ongoing USDA appropriate antibiotic use education activity is an APHIS-funded training module on antibiotic resistance currently under development at a cost of $70,400. According to agency officials, the module will be similar to CDC's online curriculum for veterinary students. It will be 1 of 19 continuing education modules for the National Veterinary Accreditation Program, which is designed to train veterinarians to assist the federal government with animal health and regulatory services. The program requires participating veterinarians to periodically renew their accreditations by completing continuing education modules online or at conferences, and participants may elect which APHIS-approved modules to take in order to fulfill their requirements. Since the APHIS module will be similar to CDC's online curriculum for veterinary students, APHIS officials told us that they will look at CDC's content to determine whether or not to incorporate it into the APHIS-funded module. APHIS officials also told us that they sought out representatives from NIFA, FDA, CDC, the American Veterinary Medical Association, and academic institutions to review the module's content, and expect the training to be available for veterinarians by June 2012. APHIS officials told us that the module on appropriate antibiotic use is not within the National Veterinary Accreditation Program's traditional scope of work. More specifically, APHIS officials are unsure how they would measure the impact of the module because, unlike the other modules in the accreditation program, it is not based on any APHIS regulatory information that can be tracked. That said, officials told us providing antibiotic use education is beneficial and will increase practitioners' awareness in this area. After the

completion of the antibiotic use module, USDA officials said they have no plans to develop new education activities.

Additional USDA-funded education activities on appropriate antibiotic use may be conducted through local extension programs. Each U.S. state and territory has a Cooperative Extension office at its land-grant university,[11] as well as a network of local or regional extension offices staffed by one or more experts who provide research-based information to agricultural producers, small business owners, youth, consumers, and others in local communities. NIFA provides federal funding to the extension system, though states and counties also contribute to the program. NIFA provides program leadership and seeks to help the system identify and address current agriculture-related issues. Two producers told us that extension programs are a helpful source of information about animal health issues. For example, they said that extension agents are very helpful in disseminating information, though their impact may be difficult to measure. In addition, they told us that when producers are successful with a preventative practice suggested by an extension agent, neighboring producers may notice and also make similar modifications, creating a multiplier effect. Two current extension agents also told us they have received inquiries from producers about antibiotic use, although these questions are not necessarily framed as appropriate use. NIFA officials told us that federally funded extension institutions submit an annual plan of work and an annual accomplishment report that provides a general overview of their yearly planned projects based on USDA priorities, but these plans are broad in nature and often do not provide details that allow NIFA to track efforts related to antibiotic use.

Producer and Veterinary Organizations' Perspectives on Federal Education Efforts

Representatives from most of the producer and veterinary organizations that we spoke with said that industry-led efforts are responsible for most of the progress made in educating producers and veterinarians in the last 10 years. For example, the National Cattlemen's Beef Association, National Milk Producers' Federation, and National Pork Board have each developed Quality Assurance programs that advise producers on their views of proper antibiotic use during production. Representatives from

[11]A land-grant university is an institution that has been designated by its state legislature or Congress to receive unique federal support, including funds for cooperative extension offices. Land-grant universities are directed by law to offer public education programs based on the results of university research, including research and education related to agriculture issues.

most of the organizations we spoke with said that the federal government should have some type of role in educating producers and veterinarians on appropriate antibiotic use, but many—including representatives from all of the producer organizations—said that they believe that these activities should be done in collaboration with industry. Representatives from most of the veterinary and producer organizations also said the federal government could improve collaboration with industry members and groups, and representatives from one veterinary organization pointed to previous federal education efforts to collect and disseminate information about avian influenza as collaborative education efforts federal agencies could model for appropriate use messages.[12] Representatives from this organization noted that such efforts included the federal government and other industry stakeholders working together and disseminating education messages to the public. They also suggested that similar efforts between the federal government, producers, and researchers could be used to educate the industry about appropriate use of antibiotics in food animals.

Regulation of Antibiotics in the EU and Denmark May Offer Lessons for the United States

Since 1995, the EU and Denmark have taken a variety of actions to regulate antibiotic use in food animals and mitigate the risk such use may pose to humans. Denmark is part of the EU and complies with EU policies but has also taken some additional actions independently. Some of the experiences in the EU and Denmark may be useful for U.S. government officials and producers, though U.S. producers face different animal health challenges and regulatory requirements than European producers.

EU and Denmark Have Taken Action to Regulate Antibiotic Use in Food Animals

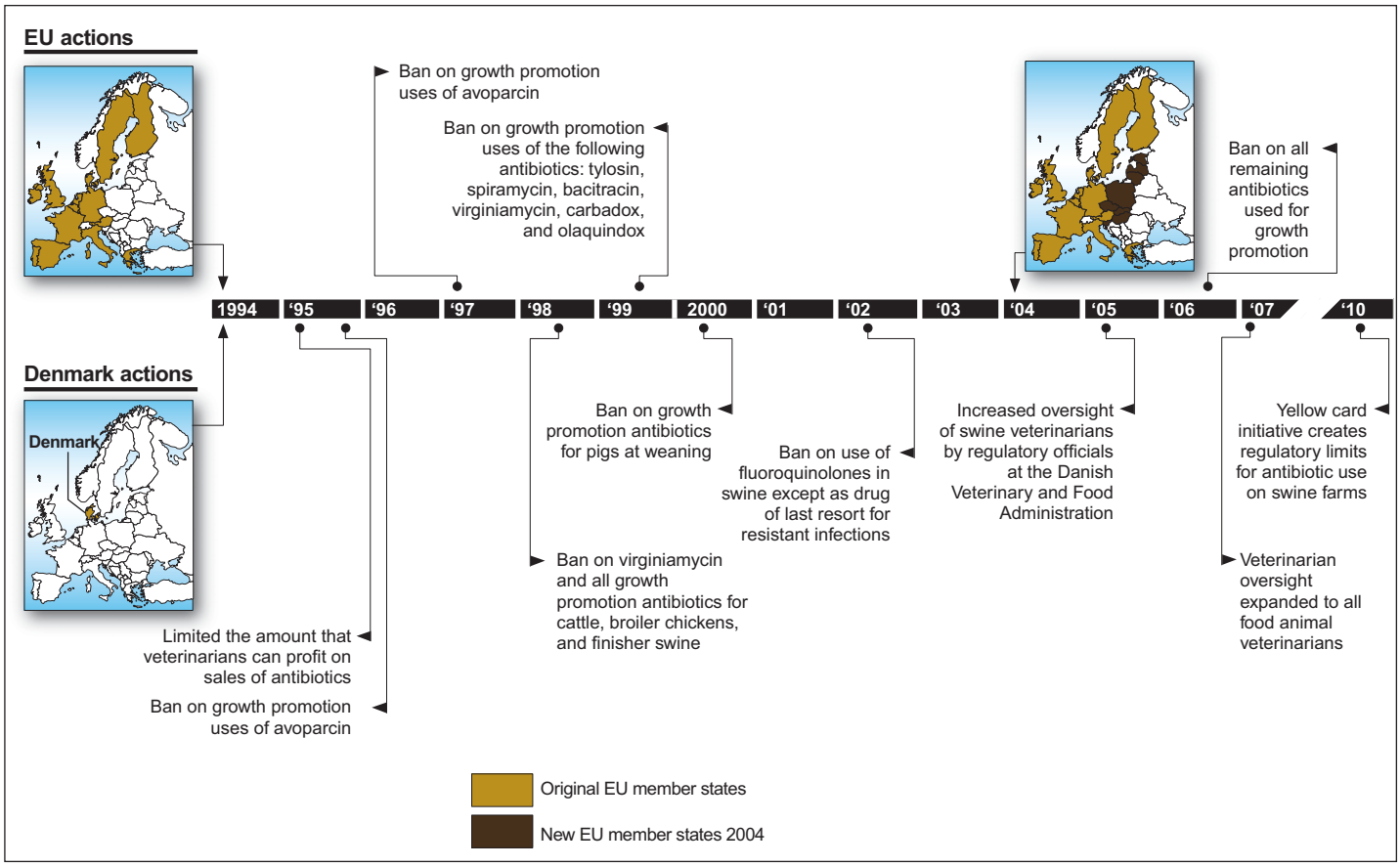
From 1995 to 2006, both the EU and Danish governments took a variety of actions to regulate antibiotic use in food animals (see fig. 2). In 1995, Denmark banned the use of avoparcin for growth promotion in food animals, and an EU-wide ban followed in 1997. Avoparcin is similar to the human medicine vancomycin, and some studies suggested that avoparcin use in food animals could be contributing to vancomycin-resistant bacteria in humans.[13] Both Denmark and the EU followed up

[12]For more information on USDA's efforts to prepare for outbreaks of highly pathogenic avian influenza, see GAO, *Avian Influenza: USDA Has Taken Steps to Prepare for Outbreaks, but Better Planning Could Improve Response*, GAO-07-652 (Washington, D.C.: June 11, 2007).

[13]Avoparcin was never approved for food animal use in the United States.

with bans on several additional growth promotion antibiotics, culminating in a total ban on growth promotion antibiotics in 2000 and 2006, respectively. Government and industry officials we spoke with in Denmark emphasized that their bans on growth promotion antibiotics began as voluntary industry efforts that were later implemented as regulations by the government.

Figure 2: EU and Denmark Actions to Regulate Antibiotic Use in Food Animals, 1994-2010



Sources: GAO analysis of EU and Denmark data; Map Resources (maps).

EU officials and both industry and government officials from Denmark said the most important factor in the development of their policies was sustained consumer interest in the issue of antibiotic use in food animals and concerns that such use could cause resistance affecting humans. In the face of these concerns, officials explained that EU policies were developed based in part on the precautionary principle, which states that

where there are threats of serious or irreversible damage, lack of scientific certainty should not postpone cost-effective measures to reduce risks to humans. Danish industry officials added that, as new data and knowledge arise, it is appropriate to reevaluate the measures taken to reduce risks. We have previously reported that the EU made other food safety decisions based on the precautionary principle, including decisions about inspecting imports of live animal and animal products, such as meat, milk, and fish.[14]

According to Danish government officials, Denmark has implemented two additional types of regulations regarding antibiotic use in food animals. First, Denmark has increased government oversight of veterinarians and producers. For example, in 1995, Denmark limited the amount that veterinarians could profit on sales of antibiotics. Then, in 2005, Denmark implemented policies requiring biannual audits of veterinarians who serve the swine industry, which Danish government officials said uses about 80 percent of all food animal antibiotics in Denmark. Government officials said these audits increase veterinarians' awareness of their antibiotic prescription patterns. In 2007 the audits were expanded to cover all food animal veterinarians. Most recently, in 2010, Denmark developed a new system—called the yellow card initiative—which sets regulatory limits on antibiotic use based on the size of swine farms. Swine farms exceeding their regulatory limit are subject to increased monitoring by government officials, which they must pay for. Danish government officials explained that the yellow card initiative is different from their past oversight efforts in that it targets producers rather than veterinarians. Second, according to Danish government officials, Denmark developed a policy to reduce veterinary use of antibiotics classified as critically important to human medicine by WHO, which like FDA, has a ranking of such antibiotics. For example, in 2002 Denmark limited veterinary prescriptions of fluoroquinolones to cases in which testing showed that no other antibiotic would be effective at treating the disease. In addition, veterinarians prescribing fluoroquinolones to food animals would need to notify government regulatory officials.

[14]GAO, *Food Safety: Selected Countries' Systems Can Offer Insights into Ensuring Import Safety and Responding to Foodborne Illness*, GAO-08-794 (Washington, D.C.: June 10, 2008).

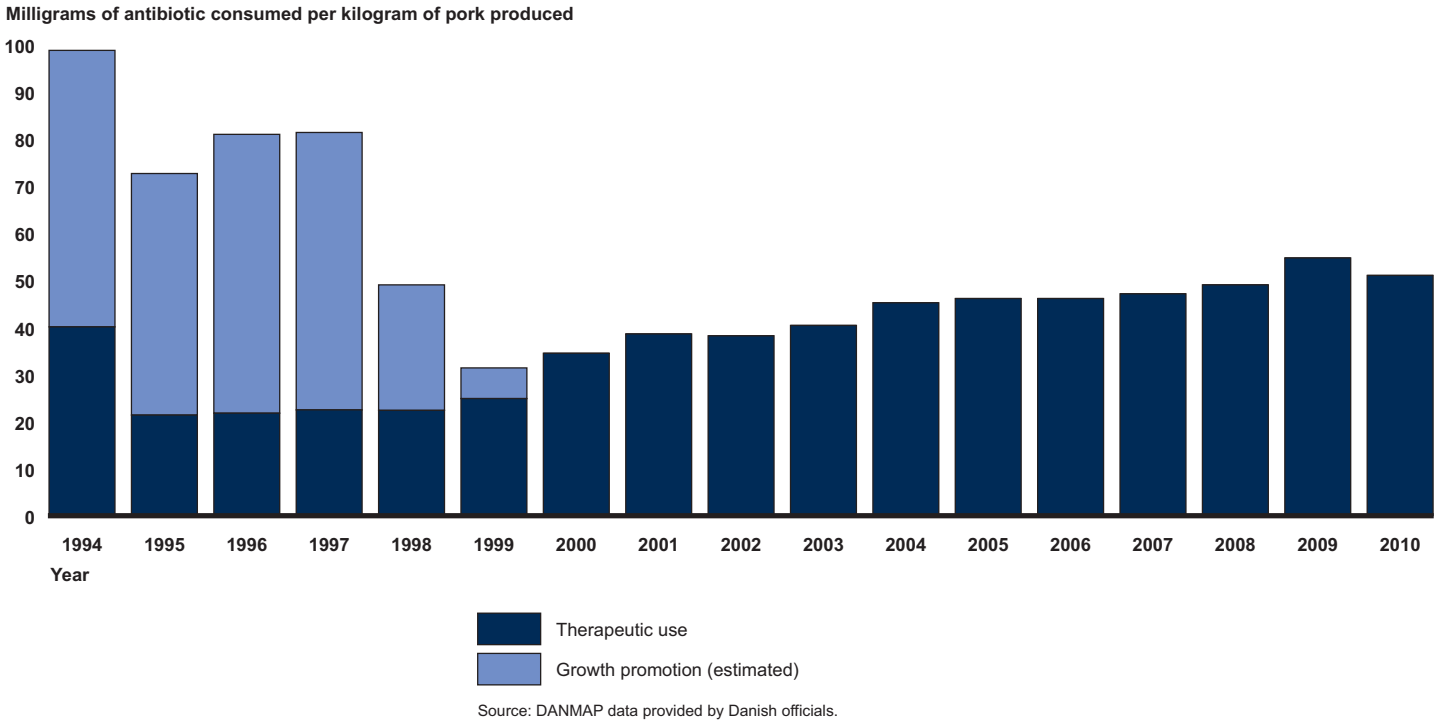
EU and Denmark Experiences Suggest Possible Lessons for the United States

U.S. producers face different animal health challenges and regulatory requirements than producers in the EU and Denmark, making it difficult to determine how effectively similar policies could be implemented in the United States. Specifically, industry officials in Denmark explained that several diseases that affect producers in the United States are no longer active in Denmark. For example, broiler chicken producers in Denmark spent many years improving their biosecurity and successfully eradicated *Salmonella*, which can cause disease both in broiler chickens and in humans, and Danish cattle producers do not have to worry about brucellosis, which has not been seen in Denmark in decades. Similarly, the regulatory environment in the EU differs from that in the United States. For example, EU countries develop and implement policies using the precautionary principle. In addition, the EU and Denmark both require prescriptions for the use of most antibiotics in animals, but the United States requires them in certain limited circumstances. Officials from HHS and USDA said they are aware of other countries' efforts to regulate antibiotic use in food animals and participate in international conferences and meetings addressing these issues. Based on the experiences in the EU and Denmark, there are several lessons that may be useful for U.S. government officials and producers.

Denmark's Antibiotic Use Data Allowed Officials to Track How Policy Changes Affected Use in Food Animals and Take Appropriate Response

According to Danish government officials, Denmark's antibiotic use data are detailed enough to allow the country to track trends in use and monitor the effects of their policies. Specifically, data show that antibiotic use in food animals declined from 1994 to 1999, but then it increased modestly from 1999 to 2009, while remaining below 1994 levels (see fig. 3). The decline coincides with the start of the changes to government policies on growth promotion and veterinarian sales profits. Danish industry and government officials noted some of the increase in antibiotic use over the last decade may be in response to disease outbreaks on swine farms. Danish government officials also mentioned, however, that the government instituted the 2010 yellow card initiative to reverse the recent increase in antibiotic use. According to these officials, antibiotic use in pig production fell 25 percent from June 2010 to June 2011 in response to the implementation of the yellow card initiative.

Figure 3: Antibiotic Use in Swine in Denmark 1994-2010



Source: DANMAP data provided by Danish officials.

Note: Between 1994 and 1999, Denmark collected data on the use of growth promotion antibiotics in aggregate, rather than by species. DANMAP officials estimated growth promotion antibiotic use in swine based on information from feed mills about the amount of feed sold and the types of growth promotion antibiotics included in the feed for the different food animal species.

Denmark Resistance Data Showed Reductions in Food Animals and Retail Meat in Most Instances

According to Danish officials, Danish data on antibiotic resistance in food animals and retail meat show reductions in resistance after policy changes in most instances. Specifically, Danish government officials have tracked resistance to antibiotics banned for growth promotion among *Enterococcus* bacteria since the mid-1990s. *Enterococcus* are commonly found in the intestinal tract of humans and food animals, making them relatively easy to track over time, though they rarely cause disease. Officials said that the percentage of *Enterococcus* from food animals that are resistant to antibiotics banned for growth promotion has decreased since the bans were implemented. Officials also mentioned declines in resistance among *Campylobacter* bacteria (which can cause foodborne illness in humans) from food animals and retail meat. For example, officials said that resistance to the critically important class of drugs called macrolides has decreased in *Campylobacter* bacteria from swine. However, Danish industry and government officials cautioned that the

association between antibiotic use and resistance is not straightforward. For example, despite restrictions on veterinary use of the critically important fluoroquinolone antibiotics since 2002, Danish resistance data have not shown a decrease in fluoroquinolone-resistant bacteria from food animals. Danish industry officials explained that restrictions on fluoroquinolone use in swine were implemented before fluoroquinolone resistance became pronounced in Denmark and that current rates of fluoroquinolone-resistant *Salmonella* in Danish pork are lower than for pork imported into Denmark.

Denmark Resistance Data Have Not Shown Decrease in Human Resistance, Except in Certain Instances

Danish officials told us that Denmark's resistance data have not shown a decrease in antibiotic resistance in humans after implementation of the various Danish policies, except for a few limited examples. Specifically, officials said that the prevalence of vancomycin-resistant *Enterococcus faecium* from humans has decreased since avoparcin was banned for use in animals in 1995. Resistance has been tracked for other types of bacteria and antibiotics, but similar declines have not been seen. Danish government officials explained that, in addition to antibiotic use in food animals, there are other important contributors to antibiotic resistance in humans, including human antibiotic use, consumption of imported meat (which may contain more antibiotic-resistant bacteria than Danish meat), and acquisition of resistant bacteria while traveling. Danish officials told us their data collection systems are not designed to gather information about whether human deaths from antibiotic resistance have fallen after the implementation of risk management policies. Officials mentioned a challenge to this type of data collection is that "antibiotic resistance" is not listed on death certificates as the cause of death; generally, as in the United States, the cause of death would be listed as multiple organ failure, making it difficult to identify deaths caused by antibiotic-resistant infections.

Danish Policies Do Not Appear To Have Led To an Increase in Bacteria That Cause Foodborne Illness

Denmark has also tracked the prevalence of bacteria that cause human foodborne illness on retail meat products, according to Danish industry officials. Producer organizations in the United States have expressed concerns that reductions in antibiotic use may lead to an increase in foodborne pathogens on meat, but industry officials in Denmark said that their data show no increase in the rates of these bacteria on meat products. These officials said, however, that several changes to management practices in slaughter plants may have helped ensure rates of foodborne pathogens on meat remained low. For example, these officials said Danish slaughter plants now use a flash-freezing technique—called blast chilling—that freezes the outer layer of an animal

carcass, reducing the number of bacteria on the meat and even killing most *Campylobacter*.

Danish Policies Affected Poultry and Swine Producers Differently

Danish producers and veterinary officials noted that the policies were easier for poultry producers to implement than for swine producers. Poultry producers had made changes to their production practices throughout the 1990s to eradicate *Salmonella* from their flocks, and these practices also helped maintain flock health without routine antibiotic use. In contrast, swine producers faced difficulties weaning piglets without antibiotics, reporting both an increase in mortality and a reduction in daily weight gain shortly after the ban. However, Danish industry officials explained that swine producers implemented multiple changes to production practices that enabled them to comply with the ban. These production practices included improved genetic selection, later weaning, improved diet, increased space per piglet, and improved flooring. Industry officials explained that such changes in production practices did have real costs to the industry. For example, weaning piglets later increases the time between litters and reduces the overall number of piglets produced annually. Despite these additional costs, however, Danish industry officials expressed pride in their ability to produce high-quality meat products while ensuring that they do not contribute unduly to the problem of antibiotic resistance.

The EU Faces Challenges but Is Working To Collect Use and Resistance Data

EU officials told us that they rely on member states to collect data on antibiotic use. As of September 2010, 10 countries in Europe collected data on sales of antibiotics used in food animals, and 5 of these countries collected species-specific data.[15] In addition, 12 other countries have recently started or planned to begin collecting antibiotic sales data.[16] Among countries that currently collect use data, these data are collected using different methods, which complicates comparing them across countries. EU officials identified several challenges to collecting information about antibiotic use throughout the EU. Specifically, identifying sources of detailed information about antibiotic use is difficult because EU countries have different distribution systems for veterinary

[15]Denmark, Sweden, France, the Netherlands and the United Kingdom collected antibiotic use data by species. Germany, Norway, Finland, Switzerland, and the Czech Republic collected more general data on antibiotic use. Norway and Switzerland are not EU countries, but they are nevertheless sharing data about antibiotic use.

[16]Austria, Belgium, Cyprus, Estonia, Hungary, Ireland, Italy, Lithuania, Luxembourg, Poland, Portugal, and Spain.

medicines and therefore collect this information in varying ways. For example, in Denmark, such data are collected from veterinary pharmacies, but not all EU countries require animal antibiotics to be dispensed through pharmacies. In addition, EU countries vary in the extent to which veterinary prescriptions are monitored electronically, making it difficult to track prescriptions consistently throughout the EU.

Despite these challenges, EU officials emphasized the importance of gathering data on antibiotic use in food animals for two reasons. First, they noted that tracking antibiotic use data allows governments to evaluate the effects of their risk management policies. Second, they mentioned that data on both antibiotic use and antibiotic resistance are needed in order to fully understand how use in animals is related to resistance in humans. Given the importance of collecting data, the EU has begun a pilot project to collect comparable antibiotic use data throughout the EU. The first phase will use a standard instrument to collect, harmonize, and analyze data on sales of veterinary antibiotics from countries that agree to participate. EU officials said that a report on sales of veterinary medicines, covering nine European countries, will be available in September 2011. EU officials said that subsequent phases will include more detailed data about species and purpose of use. They emphasized the importance of going beyond bulk sales data, noting that it is necessary to report antibiotic use in the context of the number of animals being treated or the pounds of meat produced, since it can allow for comparisons between EU countries as well as comparisons to human antibiotic use. EU officials said that the Danish system uses this type of data collection, and that WHO is working on developing guidance for how to create such data collection systems.

For resistance data, EU officials told us that the EU has been collecting information from numerous member countries and working to improve the comparability of the data between countries. In 2006, the EU produced its first report for data gathered in 2004, collating information from 26 individual countries. However, EU officials said that resistance data cannot currently be compared across countries or aggregated to provide conclusions about the entire EU, though officials are in the process of developing a report that will provide EU-wide information. Instead, officials pointed to trends identified in particular member countries. For example, officials noted a decrease in resistance in *Enterococcus* from broiler chickens after avoparcin was banned for growth promotion uses in Germany, the Netherlands, and Italy. Officials also mentioned similar declines in resistance among *Enterococcus* from healthy humans in Germany and the Netherlands.

Moreover, in addition to their data collection efforts on antibiotic use in food animals and antibiotic resistance in humans, meat, and food animals, the EU also conducts periodic baseline surveys to determine the prevalence of particular drug-resistant bacteria throughout all countries in the EU. EU officials said these baseline studies provide information that is comparable across countries. EU officials explained that EU countries are required to participate in these studies, which usually last 1 year and are used to set reduction targets for regulatory programs or to develop risk management measures. For example, in 2008 the EU conducted a prevalence study of MRSA in swine herds. It determined that the prevalence varied dramatically between member countries—it was found in more than 50 percent of swine herds in Spain, but in eight other EU countries there were no detections.

Denmark and EU Officials Emphasized Industry Role in Research

According to Danish government and industry officials we interviewed, the Danish government does not conduct research on alternatives to antibiotic use. Both industry and government officials agreed that it should be government's role to set regulatory policy and industry's role to conduct research on how to meet regulatory goals. The Danish Agriculture and Food Council—an industry organization representing producers of a variety of meat and agricultural products—has funded several studies examining alternatives to growth promotion antibiotics. For example, one such study examined the economics of five types of products that had the potential to improve feed efficiency in swine without leading to antibiotic resistance and found that few products were both economical for farmers and successful in improving feed efficiency.

EU officials also reported that at the EU-level government does not conduct a significant amount of research related to alternatives to antibiotics. They noted, however, that the EU has been trying to incentivize private industry to develop alternatives in other ways. For example, EU officials have tried to spur pharmaceutical companies to develop products to improve feed efficiency and growth by lengthening patents on such products. EU officials said that this results in a reduction in competition from generic manufacturers and has led to more than 300 applications for new feed additive products.

Conclusions

Antibiotic resistance is a growing public health problem worldwide, and any use of antibiotics—in humans or animals—can lead to the development of resistance. In 2001, USDA and HHS agencies took steps to coordinate their actions on surveillance, prevention and control of resistance, research, and product development through the 2001

interagency plan. The surveillance focus area of this plan includes action items related to improving efforts to monitor both antibiotic use in food animals, as well as antibiotic resistance in food animals and in retail meat. According to WHO, populations sampled for surveillance purposes should normally be representative of the total population—in this case, food animals and retail meat in the United States.

Since 2001, however, USDA and HHS agencies have made limited progress in improving data collection on antibiotic use and resistance. For example, although FDA has a new effort to collect data on antibiotics sold for use in food animals, these data lack crucial details, such as the species in which the antibiotics are used and the purpose for their use. The 2001 interagency plan states such data are essential for interpreting trends and variations in rates of resistance, improving the understanding of the relationship between antibiotic use and resistance, and identifying interventions to prevent and control resistance. In addition, two USDA agencies collect data on antibiotic use from food animal producers, but data from these surveys provide only a snapshot of antibiotic use practices and cannot be used to examine trends. Collecting data on antibiotic use in food animals can be challenging and costly, but without an approach to collecting more detailed data, USDA and HHS cannot track the effectiveness of policies they undertake to curb resistance. Indeed, FDA currently does not have a plan to measure the effectiveness of its voluntary strategy to reduce food animal use of antibiotics that are medically important to humans. Although there are challenges to collecting detailed data on antibiotic use, efforts are under way in the EU to begin collecting such data.

For data on antibiotic resistance, HHS and USDA agencies have leveraged existing programs to collect samples of bacteria, but the resulting data are not representative of antibiotic resistance in food animals and retail meat throughout the United States. According to the 2001 interagency plan, antibiotic resistance data will allow agencies to detect resistance trends and improve their understanding of the relationship between use and resistance. FDA is aware of the NARMS sampling limitations and has included a strategic goal of making NARMS sampling more representative and applicable to trend analysis in its draft 2011-2015 NARMS Strategic Plan. FDA officials mentioned several ways that NARMS sampling could be improved, such as discontinuing slaughter plant sampling in favor of an on-farm sampling program and increasing the number of states participating in the retail meat program.

USDA and HHS have also undertaken some research related to developing alternatives to current antibiotic use practices. However, the extent of these research efforts is unclear, as neither USDA nor HHS has assessed its research efforts to determine the progress made toward the related action item in the 2001 interagency plan. In addition, officials from most of the veterinary and several public health organizations we spoke with said that the federal government should make greater efforts to coordinate this research with the food animal industry. Without an assessment of past research efforts and coordination with industry, USDA and HHS may be limited in their ability to identify gaps where additional research is needed. In addition, USDA and HHS managers may not have the critical information they need to make decisions about future research efforts. Focus on tracking progress and making sound decisions about future research is particularly important in light of the fiscal pressures currently facing the federal government. Nevertheless, the draft 2010 interagency plan includes an action item on researching alternatives, but it does not identify steps the agencies intend to take to do so. Similarly, USDA and HHS had sought to educate producers and veterinarians about appropriate antibiotic use but did not assess their efforts. The one remaining education activity, however, is a $70,400 USDA training module on antibiotic resistance for veterinarians, which will be completed in 2012, after which there are no plans to develop new education activities.

Recommendations for Executive Action

We are making the following three recommendations:

- To track the effectiveness of policies to curb antibiotic resistance, including FDA's voluntary strategy designed to reduce antibiotic use in food animals and to address action items in the surveillance focus area of the 2001 interagency plan, we recommend the Secretaries of Agriculture and Health and Human Services direct agencies to, consistent with their existing authorities, (1) identify potential approaches for collecting detailed data on antibiotic use in food animals, including the species in which antibiotics are used and the purpose for their use, as well as the costs, time frames, and potential trade-offs associated with each approach; (2) collaborate with industry to select the best approach; (3) seek any resources necessary to implement the approach; and (4) use the data to assess the effectiveness of policies to curb antibiotic resistance.

- To enhance surveillance of antibiotic-resistant bacteria in food animals, we recommend that the Secretaries of Agriculture and Health

and Human Services direct agencies to, consistent with their existing authorities, modify NARMS sampling to make the data more representative of antibiotic resistance in food animals and retail meat throughout the United States.

- To better focus future federal research efforts on alternatives to current antibiotic use practices, we recommend that the Secretaries of Agriculture and Health and Human Services direct agencies to (1) assess previous research efforts on alternatives and identify gaps where additional research is needed, in collaboration with the animal production industry, and (2) specify steps in the draft 2010 interagency plan that agencies will take to fill those gaps.

Agency Comments and Our Evaluation

We provided the Departments of Agriculture and Health and Human Services a draft of this report for review and comment. Both departments agreed with our recommendations and provided written comments on the draft, which are summarized below and appear in their entirety in appendixes VII and VIII, respectively, of this report. The departments also provided technical comments, which we incorporated as appropriate.

In its comments, USDA agreed with our recommendations. In response to our recommendation on collecting antibiotic use data, USDA noted that the department has devised strategies to collect detailed information on antibiotic use in food animals, as documented in "A USDA Plan to Address Antimicrobial Resistance." Our report discusses many of the ongoing USDA activities described in the document, including NAHMS, ARMS, and NARMS. In commenting on our recommendation to collect more representative resistance data, USDA acknowledged that sampling for antibiotic resistant bacteria in food animals is not currently conducted on a nationally representative population, but also stated that NARMS data can still be used to examine general trends. We continue to believe that the nonrandom sampling method used for food animals in NARMS results in data that are not representative of food animals across the country and cannot be used for trend analysis. Moreover, as our report states, the NARMS program has prioritized modifying animal sampling to overcome its current biases, and both FDA and USDA have identified efforts that could be used to improve NARMS food animal sampling. In its letter, USDA identified several such efforts; we had included several of these in the draft report, and we modified the final version to include the remaining effort.

In its comments, HHS also agreed with our recommendations, but stated that FDA has made substantial progress and taken an active and deliberative role in addressing the controversial and complex issue of antibiotic use in food animals. We acknowledge that FDA has taken many actions, most of which are discussed in the report. However, as our report states, since the 2001 interagency plan, USDA and HHS agencies have made limited progress in improving data collection on antibiotic use and resistance. Specifically, as we noted in our report, FDA's data on sales of antibiotics for animal use do not include information on the species in which antibiotics are used or the purpose for their use, which, for example, prevents agencies from interpreting trends and variations in rates of resistance. Similarly, as our report states, data on antibiotic resistance from food animals are not representative and cannot be used for trend analysis—even though the 2001 interagency plan identified detecting resistance trends as an important part of monitoring for antibiotic resistance. In commenting on our recommendation regarding antibiotic use data collection, FDA recognized that having more detailed antibiotic use data would benefit its overall effort to assure the judicious use of antibiotics. FDA also noted that it is exploring potential approaches for obtaining more detailed information and that it plans to coordinate with USDA in that effort. We modified our report to include this information. In addition, regarding our findings on FDA's resistance data from retail meat, FDA stated that it does not believe samples need to be statistically representative of the entire United States to serve as indicators of U.S. retail meat. We modified our report to better reflect FDA's position, but as our report states, the FDA Science Advisory Board's 2007 review of data on antibiotic resistance in retail meat found that the lack of a national sampling strategy limits a broader interpretation of NARMS data.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, Secretaries of Agriculture and Health and Human Services, and other interested parties. In addition, this report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staff members have any questions about this report, please contact me at (202) 512-3841 or shamesl@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IX.

Sincerely yours,

Lisa Shames
Director, Natural Resources
and Environment